UNIVERSIDADE D
COIMBRA

Ricardo Jorge de Oliveira Ferreira

IMPACT OF PATIENT-REPORTED OUTCOMES IN RHEUMATOID ARTHRITIS' ASSESSMENT AND MANAGEMENT

Tese no âmbito do Programa de Doutoramento em Ciências da Saúde, Ramo de Enfermagem, orientada pelo Professor Doutor José António Pereira da Silva, pela Professora Doutora Laure Gossec e pelo Professor Doutor Mwidimi Ndosi e apresentada à Faculdade de Medicina.

Dezembro de 2019

Faculdade de Medicina
da Universidade de Coimbra

IMPACT OF PATIENT-REPORTED OUTCOMES IN RHEUMATOID ARTHRITIS' ASSESSMENT AND MANAGEMENT

Ricardo Jorge de Oliveira Ferreira

Tese no âmbito do Programa de Doutoramento em Ciências da Saúde, Ramo de Enfermagem, orientada pelo Professor Doutor José António Pereira da Silva, pela Professora Doutora Laure Gossec e pelo Professor Doutor Mwidimi Ndosi e apresentada à Faculdade de Medicina.

Dezembro de 2019

1 2 9 0

UNIVERSIDADE D
COIMBRA

This work was mostly performed in the Rheumatology Department/Clínica Universitária de Reumatologia of Centro Hospitalar e Universitário de Coimbra, E.P.E. and in the Faculty of Medicine of University of Coimbra, in association with the Health Sciences Research Unit: Nursing (UICiSA:E), Nursing School of Coimbra, Coimbra, Portugal. Part of this work was also performed in the University of the West of England, Bristol, UK, and in the Rheumatology Department of Pitié Salpêtrière Hospital and the Sorbonne Université, Paris, France.

Part of this study was financially supported by unrestricted grants: the METEOR studies were supported by the Merit Foundation (grant number RP2011-01 and RP2015-01); the RAID study was supported by EULAR (grant number CLI.013); the COMEDRA trial (NCT01315652) was supported by a grant from the French National Research Program (grant number 2010-A 01 2996-33) and an unrestricted grant from Roche; the ESPOIR cohort was created and maintained trough unrestricted grants from Merk Sharp and Dohme (MSD), Abbott, Pfizer, Roche-Chugai, INSERM, and French Society of Rheumatology. Logistical and financial support was received from Associação de Reumatologia de Coimbra (ARCo), a non-profit association of health professionals.

"— On a scale from zero to ten, how does your pain feel now? From zero to ten? In my head, past episodes gravitated, future fears, quickly invented relativities, but no number. From zero to ten, ten meaning a very strong pain, he explains. You don't have to tell me that, I know what you mean. However, standing between me and my answer, is this modulated learning over the years: I can always put up with more pain. Or at least, I think I can.

— If you do not know how to answer, the pain is certainly not very intense.

How mistaken you are, doctor, and how it hurts to see your nearly scoffing smile. How mistaken you are if you think that, to help me, you direct your look at the computer screen or your cards, impatient for a precise reply that is so difficult to give.

— Seven — I reply, without being certain, just to get him to change his expression, to avoid seeing his disrespect for the days spent worrying, for the days fighting against an illness that will follow me forever. — Seven.

— But how can you have such pain if you are taking this medication?!

The pain now becomes more intense. Not just the physical pain, the other also. The pain of always being so fatigued. (...)"

Margarida Fonseca Santos

In: “From zero to ten”. Lisboa: Clube do Autor, 2015

ABSTRACT

Rheumatoid arthritis (RA) is a systemic chronic inflammatory disease that affects approximately 0.5 to 1.0% of the adult population. It can cause severe pain, stiffness and fatigue, and lead, over the years, to joint deformity, disability and premature death. The current treatment of RA is guided by quantified clinical assessment of disease activity and aims to achieve a state of remission as soon as possible. This strategy is known as treat-to-target (T2T), the prime target being “remission”. The definition of remission is based on tender and swollen 28-joint counts (TJC28/SJC28), laboratory markers of inflammation such as C-reactive protein (CRP) level or erythrocyte sedimentation rate (ESR), and by the physician’s and patient’s global assessment (PhGA/PGA) of disease activity. Current remission criteria for RA, developed by the American College of Rheumatology (ACR) and by the European League Against Rheumatism (EULAR), include a Boolean version based on very low thresholds for 4 variables (or "4v-remission"), i.e. SJC28, TJC28, CRP (in mg/dL), and PGA (here scored 0-10) must all be ≤1.

PGA is the only patient-reported outcome measure (PROM) considered in these indices and consists of a single question assessing patient's perception of disease/arthritis activity on a 0 to 100 mm visual analogue scale (100=worst). PGA is, by far, the most frequent single item impeding patients from reaching the target of remission, a status designed as “PGA-near-remission”.

Our research group hypothesised that PGA does not adequately represent disease activity closely enough to merit inclusion in the definitions that guide pharmacological disease management decisions, especially immunosuppressive therapy, thus representing a potential risk for both the quality and safety of care. To test our hypotheses we conducted different cross-sectional and longitudinal studies, using data from patients with RA followed in clinical practice cohorts and included in randomized controlled trials (RCTs) of biological agents, in an intense international collaboration.

Our initial work was directed towards the lack of standardization of the PGA question: we explored whether using each of five different formulations of the PGA question has a significant influence on the proportion of patients achieving remission. Differences of up to 6.3% in remission were attributable to the PGA formulation, in a sample of 191 patients from the “Coimbra RA cohort” (CoimbRA). A mixed-methods study then aimed to better understand the patients’ perspectives about the meaning and purpose of PGA. Using interviews and focus groups (n=33, CoimbRA) we concluded that many patients were unaware of PGA’s purpose and more importantly, uncertainties and misconceptions on its meaning were frequent, thus undermining the validity of the measure. We also demonstrated that a structured explanation to the patients by the nurse, about the intended purpose of PGA is feasible and may improve its validity. Both these studies supported the need for the standardization of PGA and patient’s education on its use.

Then, we aimed at determining the influence of PGA on the frequency of RA remission, and understanding how PGA correlates with a broad array of variables, from disease activity to comorbidities and psychological dimensions, at different levels of disease activity. Using cross-sectional studies, we showed that the proportion of patients failing 4v-remission solely due to a PGA>1/10 was 37.2%, 19.1% and 10.0%, respectively for the CoimbRA cohort (n=309), for a European (n=1,588) and for a large International cohort (METEOR, n=27,768). These rates were up to threefold the "full" 4v-remission status. Second, the three studies confirmed that PGA is more strongly associated with both physical (e.g. function, pain, physical well-being) and psychological/personality aspects of disease impact, as well as comorbidities (e.g. fibromyalgia or osteoarthritis), than with "inflammation". This is especially true in the lower levels of disease activity, where the definition of the target is more decisive. Thus, control of inflammation (4v- or PGA-near-remission states) does not equate to a low impact of the disease upon patients' lives.

In the last set of studies, we explored whether excluding PGA from the definition of the target has a significant impact on its ability to predict and ascertain future functional and radiographic outcomes – the core objectives of the T2T concept. Using the METEOR cohort (n=32,915), we determined that the most stringent definitions of remission, which include PGA, were associated with better function, albeit with no statistically relevant differences between definitions of remission. It was also demonstrated that being in clinical remission does not equate to having a good physical function. To assess the association between PGA and radiographic progression we performed two analyses. Using data from an early RA cohort (ESPOIR, n=520), we found no statistically significant relationship between PGA and radiographic damage over 3 years, at an individual level. However, the proportion of patients with damage progression (>5 points) was lower in 4v-remission (29%) than with PGA-near-remission (45%). We performed an individual patient meta-analysis from 11 RCTs including 5,792 patients. The conclusion was that 4v-remission and PGA-near-remission (or a combination of both: 3v-remission, i.e. excluding PGA) had similar probabilities of achieving a good radiographic outcome.

All these observations led us to propose that the current definition of remission, which includes PGA, is not the most adequate to define the target for immunosuppressive therapy. We propose, a dual T2T approach, separating objective inflammatory signs and patient-reported impact targets. The first target is adequately conveyed by the 3v-remission (excluding PGA) and is appropriate to guide the process and doctor-centered immunosuppressive therapy. The second target should be served by measures that allow understanding the domains of impact thus providing guidance to personalized adjunctive interventions.

The role of an articulated multi-professional teamwork in optimizing these treatment aims is the objective of a final integrative paper. We believe that the work presented in this thesis can be seen as a basis and inspiration to foster the change of treatment paradigms in chronic diseases towards more person-centered care.

RESUMO

A artrite reumatóide (AR) é uma doença inflamatória crónica sistémica que afeta aproximadamente 0,5 a 1,0% da população adulta. Pode causar dor, rigidez e fadiga acentuadas e levar, ao longo dos anos, à deformidade articular, incapacidade e morte prematura. O tratamento atual da AR é orientado pela avaliação clínica quantificada da atividade da doença e visa alcançar um estado de remissão o mais precoce possível. Esta estratégia é conhecida como *treat-to-target* (T2T), sendo o *target* (ou "alvo" terapêutico) principal a "remissão". A definição de remissão é baseada na contagem de 28 articulações dolorosas (*tender joint count,* TJC28) e tumefactas (*swollen joint couns,* SJC28), marcadores laboratoriais de inflamação como o nível de proteína C-reativa (PCR) ou a velocidade de sedimentação eritrocitária, e pela avaliação global da atividade da doença pelo médico e pelo doente (PhGA e PGA). Os atuais critérios de remissão para AR, desenvolvidos pelo *American College of Rheumatology* (ACR) e pela *European League Against Rheumatism* (EULAR), incluem uma versão booleana baseada em limiares muito baixos para 4 variáveis (ou "remissão 4v"), ou seja, SJC28, TJC28, PCR (em mg/dL) e PGA (pontuado de 0 a 10), todos eles devendo ter pontuação ≤1.

O PGA é o único *patient-reported outcome* (PRO) considerado nestes índices e consiste numa única questão que avalia a perceção do doente sobre a atividade da doença/artrite numa escala visual analógica de 0 a 100 mm (100=pior). O PGA é, marcadamente, o item individual que mais influencia o alcance do *target* remissão, um estado por nós designado como “*PGA-near-remission*”.

O nosso grupo de investigação colocou em hipótese que o PGA não representa a atividade da doença de forma suficientemente próxima para merecer ser incluído nas definições que orientam as decisões de controlo da doença, nomeadamente para ajuste de terapêutica imunossupressora, representando assim um risco potencial tanto para a qualidade como para a segurança dos cuidados. Para testar as nossas hipóteses, realizámos diferentes estudos transversais e longitudinais, utilizando dados de doentes com AR seguidos em coortes da prática clínica de ensaios clínicos randomizados (ECR) de agentes biológicos, numa intensa colaboração internacional.

O trabalho inicial foi direcionado para a falta de padronização da questão do PGA: explorámos se o uso de cada uma das cinco diferentes formulações do PGA tem uma influência significativa na proporção de doentes que alcançam a remissão. Numa amostra de 191 doentes da "*Coimbra RA cohort*" (CoimbRA) verificaram-se diferenças de até 6,3% na taxa de remissão, devidas à formulação do PGA. Um estudo de métodos mistos teve então como objetivo compreender as perspetivas dos doentes sobre o significado e a finalidade do PGA. Através de entrevistas e grupos focais (n=33, CoimbRA). Concluímos que muitos doentes

desconheciam a finalidade do PGA e, mais importante, eram frequentes as dúvidas e equívocos sobre o seu significado, comprometendo assim a validade da medida. Demonstrámos também que uma explicação estruturada aos doentes pelo enfermeiro, sobre o objetivo pretendido e significado do PGA é exequível e pode melhorar a sua validade. Ambos os estudos apoiaram a necessidade da padronização do PGA e da educação do doente sobre o seu uso.

Em seguida, procurámos determinar a influência do PGA na frequência da remissão da AR e compreender como é que o PGA se correlaciona com um vasto leque de variáveis, desde a atividade da doença, às comorbilidades e dimensões psicológicas, nos diferentes níveis de atividade da doença. Utilizando estudos transversais, verificou-se primeiramente que a proporção de doentes que não atinge a remissão 4v apenas devido a um PGA>1/10 foi de 37,2%, 19,1% e 10,0%, respetivamente para a coorte CoimbRA (n=309), para uma coorte europeia (n=1.588) e para uma grande coorte internacional (METEOR, n=27.768). Estas taxas representam até três vezes a taxa de remissão 4v. Em segundo lugar, os três estudos confirmaram que o PGA está mais fortemente associado a aspetos físicos (por exemplo, função, dor, bem-estar físico) e psicológicos/personalidade respeitantes ao impacto da doença, bem como a comorbilidades (por exemplo: fibromialgia ou osteoartrose), do que associado à "inflamação". Isto é especialmente verdade nos níveis mais baixos de atividade da doença, onde a definição do *target* é mais decisiva. Assim, o controlo da inflamação (estar em remissão 4v ou em *PGA-near-remission*) não equivale a que os doentes sintam um baixo impacto da doença nas suas vidas.

No último conjunto de estudos, explorámos se a exclusão do PGA da definição do *target* tem um impacto significativo na sua capacidade de prever e determinar a capacidade funcional/física e a progressão de dano articular radiográfico - os objetivos centrais do conceito T2T. Utilizando a coorte METEOR (n=32.915), determinou-se que as definições mais restritas de remissão, que incluem o PGA, estavam associadas a uma melhor capacidade funcional, embora sem diferenças estatisticamente relevantes entre as definições de remissão. Também foi demonstrado que estar em remissão clínica não equivale a ter uma boa função física. Para avaliar a associação entre o PGA e a progressão radiográfica foram realizadas duas análises. Utilizando dados de uma coorte de AR precoce (ESPOIR, n=520), não encontrámos relação estatisticamente significativa entre o PGA, isoladamente considerado, e a progressão de dano radiográfico em 3 anos. No entanto, a proporção de doentes com progressão do dano articular (>5 pontos) foi menor nos doentes em remissão 4v (29%) comparativamente aos doentes em *PGA-near-remission* (45%). Realizámos ainda uma análise semelhante usando dados individuais dos doentes de 11 ECRs e 5.792 doentes. A conclusão foi que a remissão 4v e o *PGA-near-remission* (ou ainda uma combinação de ambos os grupos: remissão 3v, o que equivale a excluir o PGA) tiveram probabilidades semelhantes de alcançar um bom *outcome* radiográfico.

Todas essas observações levaram-nos a defender que a atual definição de remissão, que inclui o PGA, não é a mais adequada para definir o *target* da terapia imunossupressora. Propusemos, ao invés, uma abordagem de duplo T2T, separando sinais inflamatórios objetivos de medidas (subjetivas) de impacto relatadas pelo doente. O primeiro *target* é adequadamente veiculado pela remissão 3v (excluindo o PGA) e é adequado para orientar o processo e a terapêutica imunossupressora, centrada no médico. O segundo *target* deve ser acompanhado de medidas que permitam compreender os domínios de impacto na vida da pessoa, fornecendo assim orientação precisa para implementar intervenções adjuvantes personalizadas.

O papel de uma equipa multiprofissional, devidamente articulada, na otimização do atingimento desses *targets* de tratamento é o assunto abordado numa publicação final integrativa, apresentada no final desta tese. Acreditamos que o trabalho aqui apresentado pode ser visto como uma base e inspiração para promover uma mudança nos paradigmas de tratamento das doenças crónicas em geral e para a consecução de cuidados mais centrados na pessoa.

THESIS OUTLINE

This Thesis is organised in six chapters. It includes twelve paper manuscripts, six of which report original research and one a protocol for an individual patient data meta-analysis, all published in international, peer-reviewed journals indexed in Web of Science; two are scientific correspondence letters published in the two top ranking journals in rheumatology. Three of the manuscripts are in the final stages of work for submission. They are included because they are in very advanced stages of revision by the co-authors, and because they represent important pieces of the work performed, contributing significantly to the coherence and reach of the thesis. Time constraints for the thesis submission did not allow us to wait for their publication, as we would have wished.

Chapter I presents a general introduction to rheumatoid arthritis (RA), its epidemiological features, pathogenesis and risk factors, clinical manifestations and disease impact, as well as current classification criteria and diagnosis, treatments and management strategies. It also covers the relevance of patient-reported outcome measures (PROMs) and the role of nurse in the management of RA. This chapter, conveying the state of knowledge at the start of this doctoral program, ends with the aims of this thesis.

Chapter II includes two published manuscripts, using data from patients with RA, and addresses the importance of the standardisation of patient global assessment (PGA) formulation and application. In **Manuscript 1**, we investigated how five different PGA formulations used in four disease indices affect the remission rates in patients with RA (n=191). In **Manuscript 2**, through interviews with patients (n=33), we explored their reasoning and difficulties while completing three different formulations of PGA. We also assessed the impact of a structured explanation, provided by the nurse, on what PGA is meant to represent and its intended use. The impact of the structured explanation was assessed in terms of change in the scores and in the rate of remission.

Chapter III comprises three published manuscripts, which had two main objectives: (i) to explore the physical, psychological, clinical and contextual determinants of PGA, and (ii) to determine the proportion of patients who fail Boolean remission solely due to PGA. These manuscripts used data from patients attending different clinical practice settings: Coimbra (n=309; **Manuscript 3**), Coimbra, France and twelve European Countries (n=1588; **Manuscript 5**), and a multinational database (METEOR cohort) with 32 countries, including India, Portugal, Italy and Netherlands as the most representative ones (n=27,768, **Manuscript 6**). This chapter also includes a correspondence letter (**Manuscript 4**), in response to a “Views and News” article in Nature Review’s in Rheumatology which discussed namely our proposal to replace the current treat-to-target (T2T) by a dual T2T paradigm, firstly presented in **Manuscript 3**.

Chapter IV includes two published manuscripts and two in preparation, studying the longitudinal association between PGA and the two main outcomes in RA that the concept of remission is expected to predict: physical function and radiographic damage progression. In **Manuscript 7,** we describe the association between seventeen definitions of remission (which include PGA, with different weights) with functional status. For this purpose we used the METEOR cohort (n=32,915). In **Manuscript 8**, we used data from a French multi-centre prospective observational study (ESPOIR), to compare the association between achieving 4v-remission and PGA-near-remission during the first year of follow-up, with structural progression over three years, in patients with early arthritis (n=520). We also explored the association of each individual component of the Boolean definition with radiographic damage. In **Manuscript 9**, we present the protocol for a meta-analysis, using individual patient data from randomised clinical trials, aimed at analysing the impact of excluding PGA from the definition of remission on its ability to predict long-term physical function and radiographic damage. **Manuscript 10** is the first manuscript resulting from this individual patient data meta-analysis, for which we were able to consider data from 5,792 patients with RA included in 11 randomized-controlled trials of biological agents. It presents results on the two-year prediction of radiographic damage progression, comparing mutually exclusive remission states, i.e. 4v-remission versus PGA-near-remission, PGA-near-remission versus non-remission, as well as comparing the accuracy performance of the current 4v-remission and of the proposed 3v-remission, both against non-remission status.

Chapter V summarizes the implications of our work for patient care and for nursing, not only in the rheumatology field but in the overall chronic patient care. It includes one published letter and one manuscript in preparation. In **Manuscript 11**, in a letter stimulated by an article on the risk of overtreatment in rheumatology, we further clarify the dual T2T proposal, highlighting how it might reduce the risk of overtreatment and, concomitantly, enhancing the achievement of goals relevant to patients. In **Manuscript 12**, we build on the evidence included in this thesis, to propose a model of multi-professional care aimed at optimizing person-centered outcomes with a central role for nurses not only in RA but in the general field of chronic disease management. Here, we also detail our proposed model of dual T2T, namely how to address both clinical treatment targets and personal goals, using shared decision-making.

Finally, **Chapter VI** is dedicated to the combined discussion of all studies, considering the strengths and limitations of the research findings, their potential implications in an integrated perspective, while identifying potential areas for further work.

LIST OF ACRONYMS

ACR – American College of Rheumatology
CDAI – Clinical Disease Activity Index
CoimbRA – Coimbra Rheumatoid Arthritis' cohort
CRP – C-Reactive Protein
DAS28 – Disease Activity Score using 28 joint counts
DMARD – Disease-Modifying Anti-Rheumatic Drug
ESR – Erythrocyte Sedimentation Rate
EULAR – European League Against Rheumatism
GRO – Good Radiographic Outcome
LDA – Low Disease Activity
mTSS – modified Total Sharp Score
NSAID – Non-Steroidal Anti-Inflammatory Drug
OMERACT – Outcome Measures in Rheumatology
PGA – Patient Global Assessment of disease activity
PhGA – Physician/evaluator Global Assessment of disease activity
PROM – Patient-Reported Outcome Measure
QoL – health-related Quality of Life
RA – Rheumatoid Arthritis
RAID – Rheumatoid Arthritis Impact of Disease score
RCT – Randomized Controlled Trial
SDAI – Simplified Disease Activity Index
SJC8 – Swollen Joint Counts in 28
T2T – Treat-to-Target strategy
TJC8 – Tender Joint Counts in 28
VAS – Visual Analogue Scale

4V-remission – remission using 4 variables: SJC28, TJC28, CRP, and PGA, all ≤1
3V-remission – remission using 3 variables: SJC28, TJC28, and CRP, all ≤1
PGA-near-remission – near 4V-remission: SJC28, TJC28, and CRP, all ≤1 and PGA >1
Non-remission – SJC28 >1, or TJC28>1, or CRP >1

TABLE OF CONTENTS

Chapter I

GENERAL INTRODUCTION

GENERAL INTRODUCTION

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is one of the most prevalent chronic inflammatory diseases, affecting approximately 5 to 10 per 1000 adults in Western countries.[1-3] It primarily involves the joints, causing pain, stiffness, loss of mobility and, with time, cartilage and bone damage leading to persistent disability. The disease may also involve extra-articular manifestations (e.g. rheumatoid nodules, pulmonary involvement or vasculitis), and systemic comorbidities (e.g. cardiovascular disease).[4]

In the last two decades, the ability to effectively halt the progression of RA before irreversible joints damage occurs has increased dramatically, thanks to the advent of novel therapeutic agents, the development of new classification criteria allowing for earlier diagnosis, the earlier introduction of disease-modifying therapy, the adoption of a tighter control of disease activity and the establishment of disease remission (or at least low disease active) as the treatment target to be attained as early and consistently as possible.[4 5] The prospects for most patients are now favourable. However, many patients still do not respond as desired, not only in terms of efficacy in lowering disease activity and preventing functional and structural deterioration,[3 4] but also in terms of symptom severity, such as pain, fatigue, physical function, or emotional well-being.[6] The burden for both the individual and society is therefore still substantial, due to major direct medical costs, reduced work capacity, decreased societal participation and quality of life,[4 7] justifying the need for further investigation.

Epidemiology

In Western countries, where most epidemiological studies in RA have been done, its estimated prevalence varies between 0.5 to 1.0% in white adult individuals.[1-3] The prevalence of RA seems to have relevant geographic and ethnic differences,[3,4] with an apparent reduction from north to south (in the northern hemisphere) and from urban to rural areas.[8 9] These variations are considered indicative of differences in the genetic background and environmental exposures.[10] The disease is three times more frequent in women than in men and its prevalence rises with age, reaching the peak in women older than 65 years.[11] In the Portuguese adult population, the prevalence of RA has been estimated at 0.7% (95%CI 0.5 to 0.9%), with a fourfold higher prevalence for women (1.2%; 0.8 to 1.5%) compared to men (0.3%; 0.1 to 0.4%).[12]

Pathogenesis and risk factors

A key feature of RA is the chronic inflammation of the synovial membrane (synovitis) in multiple joints (joint swelling), which can destroy articular cartilage and juxta-articular bone (structural damage).[5] Synovitis is a consequence of immune activation reflected by a transendothelial influx and/or local activation of a variety of mononuclear cells, such as T cells, B cells, plasma cells, dendritic cells, macrophages and mast cells.[13] Neovascularization (growth of new blood vessels) is another hallmark of RA synovitis.[5] The lymphoid infiltrate can be diffuse or, commonly, form lymphoid-follicle-like structures. The destruction of bone by the synovial membrane, mediated by the osteoclast, leads to bone erosions typically situated at the cartilage–bone–synovial membrane junction, a cardinal sign of RA. Enzymes produced by neutrophils and synoviocytes, directly contribute to bone and cartilage destruction, while cytokines secreted by a large number of inflammatory cells, such as interleukin 1 and TNF-α, stimulate bone and cartilage cells to reduce the production of tissue matrix and increase its active degradation.[13]

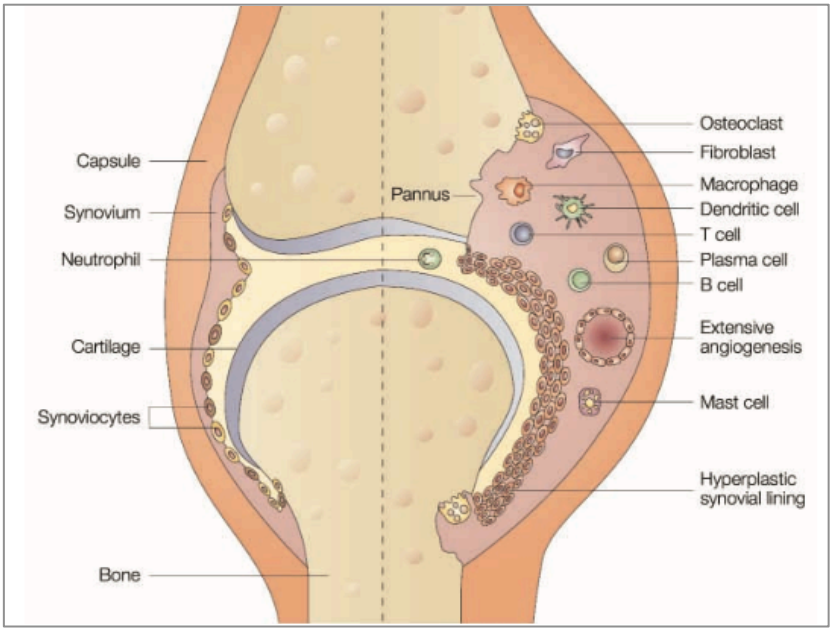


Figure 1. Schematic view of a normal joint and its changes in rheumatoid arthritis

Figure reproduced from: Smolen JS, Steiner G. Therapeutic strategies for rheumatoid arthritis. *Nat Rev Drug Discov* 2003;2(6):473-88.[13]

The aetiology of RA remains unclear. Current evidence suggests that multiple factors are involved, whereby an initial combination of environmental, lifestyle, and randomly determined insults occurring in a genetically predisposed, and/or epigenetically modified individual leads to breach of immunological tolerance and initiation of the autoimmune aggression (Figure 2).[4] An additional trigger, perhaps infectious, drives expansion of T-cell-mediated autoimmunity, and subsequent articular focalization via mechanisms that are currently

unintelligible (e.g., neurological, vascular, biomechanical).[4]

Genetic factors, especially related to the HLA-DRB1 gene locus, are preponderant for the risk of RA, with a positive family history increasing the risk of the disease by three to five fold.[4] Being female is also associated with around to three fold increase in the risk of RA.[3]

Among the environmental risk factors, smoking is the most important one, conferring a 20 to 40 fold risk increase.[14] Other potential environmental risk factors include dust inhalation (e.g. pulverized cement, silica, asbestos, glass fibres and other materials), infectious agents (e.g., Chikungunya virus or Epstein–Barr virus), vitamin D deficiency, alcohol intake, coffee intake, oral contraceptive use, obesity, changes in the microbiota (namely periodontal and gut microbiota), and low socioeconomic status, including low educational level.[3,10]

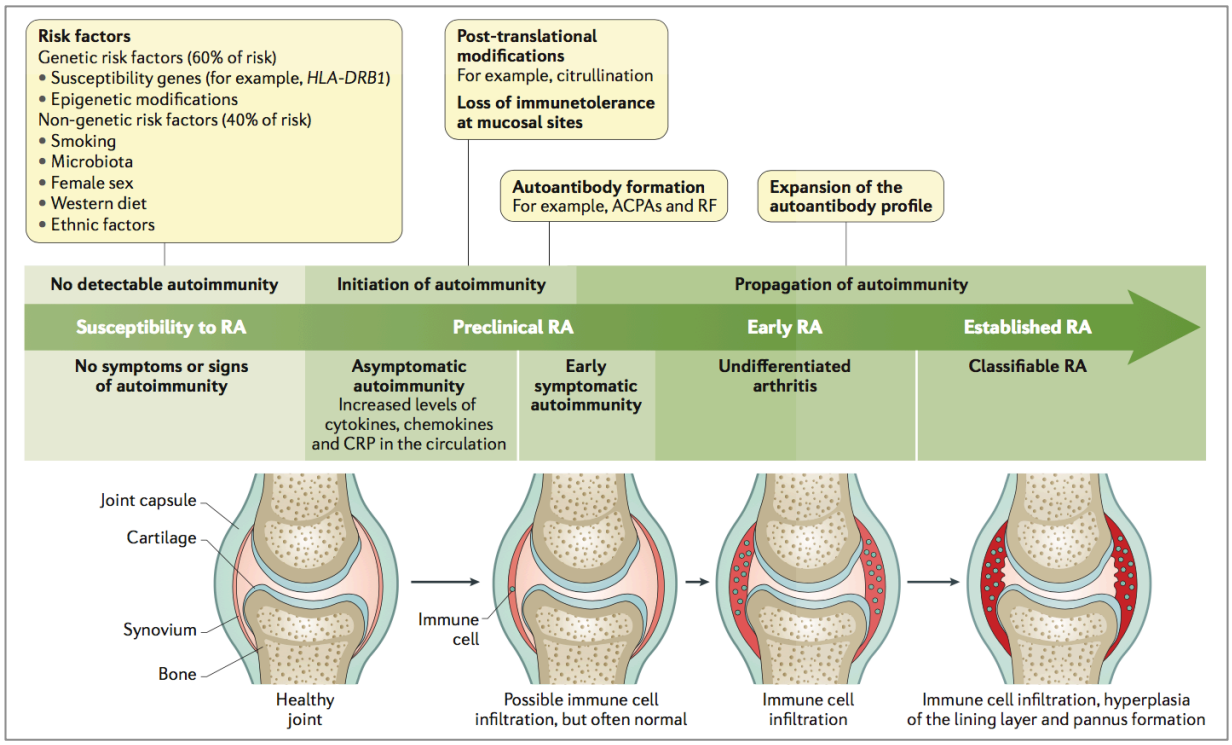


Figure 2. Development and progression of rheumatoid arthritis

Figure reproduced from: Smolen JS, Aletaha D, Barton A, et al. Rheumatoid arthritis. Nat Rev Dis Primers 2018;4:18001.[3]

Legend: ACPA, anti-citrullinated protein antibody; CRP, C-reactive protein; RF, rheumatoid factor.

Clinical manifestations and disease impact

The lifetime manifestations and consequences of RA are very wide, from symptoms and signs circumscribed to the joint to extra-articular and systemic manifestations, and complications of treatment, leading to increased overall mortality.

RA typically presents as a chronic, persistent, symmetric, peripheral polyarthritis, with a fluctuating course in terms of intensity. Synovitis causes pain, stiffness and soft joint swelling, typically starting in the small joints of the hands and feet, bilaterally, and progressing to other more proximal joints. The distal interphalangeal joints are usually spared, the same happening with the spine, with a single important exception for the atlantoaxial (C1-C2) joint.[3 5] In active phases of the disease, disabling early morning stiffness may last up to several hours. With persistent inflammation, the majority of patients will develop cartilage loss and bone erosions with ensuing and increasing deformity, disability, and pain, which is no longer dependent on inflammation but rather due to irreversible structural damage.[15] During the natural course of the disease, symptoms and disability are predominantly due to inflammation in the early stages of the disease and to damage accrual in advanced disease.[16]

As a systemic inflammatory disease, RA can lead to a number of extra-articular manifestations which affect up to 30% of patients, more commonly involving the eyes, lungs, heart and blood vessels.[3,17] A list of most common extra-articular features is presented in Table 1.[10] Rheumatoid nodules are the most frequent extra-articular manifestation. They usually present as firm lumps located subcutaneously near bony prominences such as the elbow , but may also affect internal organs such as the lungs and the heart . More detrimental are interstitial lung disease or vasculitis,[4 5] although their frequency is much lower and declining.[18] Patients with RA also have a higher prevalence of multiple comorbidities (Table 1).[10] Among these are ischemic cardiovascular diseases, the primary cause of death in people with RA, which are more closely associated with disease activity than with traditional cardiovascular risk factors.[19] The risk of cardiovascular and other comorbidities has been significantly reduced with modern therapeutic strategies leading to good control of the disease process.[20-22] However, it is also important to highlight that some comorbidities are associated with treatments. Examples include osteoporosis and cataract (steroids), gastrointestinal ulceration (non-steroidal anti-inflammatory drugs), and infections and melanoma (biological agents and steroids).[10] Fibromyalgia, not referred in Table 1 is also an important and frequent comorbidity of RA.[23 24]

Extra-articular disease	Comorbidities
• Nodules • Pulmonary - Pulmonary nodules - Pleural effusion - Fibrosing alveolitis • Ocular - Keratoconjunctivitis sicca - Episcleritis - Scleritis • Vasculitis - Nail fold - Systemic • Cardiac - Pericarditis - Pericardial effusion - Valvular heart disease - Conduction defects • Neurological - Nerve entrapment - Cervical myelopathy - Peripheral neuropathy - Mononeuritis multiplex • Cutaneous - Palmar erythema - Pyoderma gangrenosum - Vasculitic rashes - Leg ulceration • Amyloidosis	• *Cardiovascular* - Myocardial infarction - Heart failure - Stroke - Peripheral vascular disease - Hypertension • *Cancer* - Lymphoma and lymphoproliferative diseases - Lung cancer - Skin cancer • *Infection* - General - Bacterial • *Other* - Depression - Gastrointestinal disease - Osteoporosis - Psoriasis - Renal disease Some comorbidities are mainly associated with rheumatoid arthritis (eg, cardiovascular), some with treatment (eg, gastrointestinal disease), and some with both disease and treatment (eg, infection).

Table 1: Common extra-articular manifestations and comorbidities in rheumatoid arthritis

Adapted from: Scott DL, Wolfe F, Huizinga TW. Rheumatoid arthritis. Lancet 2010;376(9746):1094-108.[10]

RA can have a profound impact upon individuals and society at large. Pain and fatigue can be overwhelming symptoms in RA, inducing suffering and significantly interfering with physical functioning, ability to work and to socialize, thus leading to poorer health-related quality of life (QoL), both in physical and mental components.[6 7 25-27]

In the Portuguese population it was found that RA was significantly and independently associated with worse QoL, being among rheumatic and musculoskeletal diseases the second with greater effect, after polymyalgia rheumatica and before fibromyalgia.[12] A similar trend was observed for the association with physical function.[12]

Severe disability has high health-care expenses to families and society, which increase with the disease duration.[10 28 29] The treatment-costs are very relevant, namely with biologic and targeted disease-modifying antirheumatic drugs (DMARDs). Prices vary with region and country, ranging between $10 000 (Europe) to $36 000 (United States) annually per patient.[5]

An analysis performed in 2008 estimated the total costs of RA to society at €45.3 billion in Europe and €41.6 billion in the United States.[3 30] These costs are however being reduced in many countries with the advent of equally effective and significantly more affordable biosimilar DMARDs.[3, 5]

Patients with rheumatoid arthritis continue to have increased rates of overall mortality, mostly from cardiovascular disease and infection.[10 31-33] A prospective analysis of the Nurses' Health Study reported that women with RA had a significantly increased risk of total mortality (HR=1.40; 95%CI 1.25 to 1.57) compared with those without RA. The risk of death due to respiratory (Hazard Ratio, HR=2.06; 95%CI 1.51 to 2.80) and cardio-vascular diseases (HR=1.45; 95%CI 1.14 to 1.83) were particularly increased, while mortality associated with cancer was not (HR=0.93; 95%CI 0.74 to 1.15).[34] Premature mortality has also been reduced with current treatment strategies.[3, 35]

Classification criteria and diagnosis

Although no diagnostic criteria exist for RA, classification criteria that include clinical manifestations and serological markers (autoantibody and acute-phase reactant levels) inform clinical diagnosis.[3] Whereas diagnosis has the ultimate goal of being correct at the level of the individual patient, classification aims to maximize homogeneous populations for study purposes.[4] In 1987 classification criteria were established by the American College of Rheumatology (ACR),[36] designed to distinguish established RA from other types of joint diseases (Figure 3).[10] However, their usefulness was limited by poor sensitivity in early stages of the disease.[37] New classification criteria, designed to allowing earlier identification of the condition, were developed by the ACR and European League Against Rheumatism (EULAR) and published in 2010[38] (Figure 3).[10]

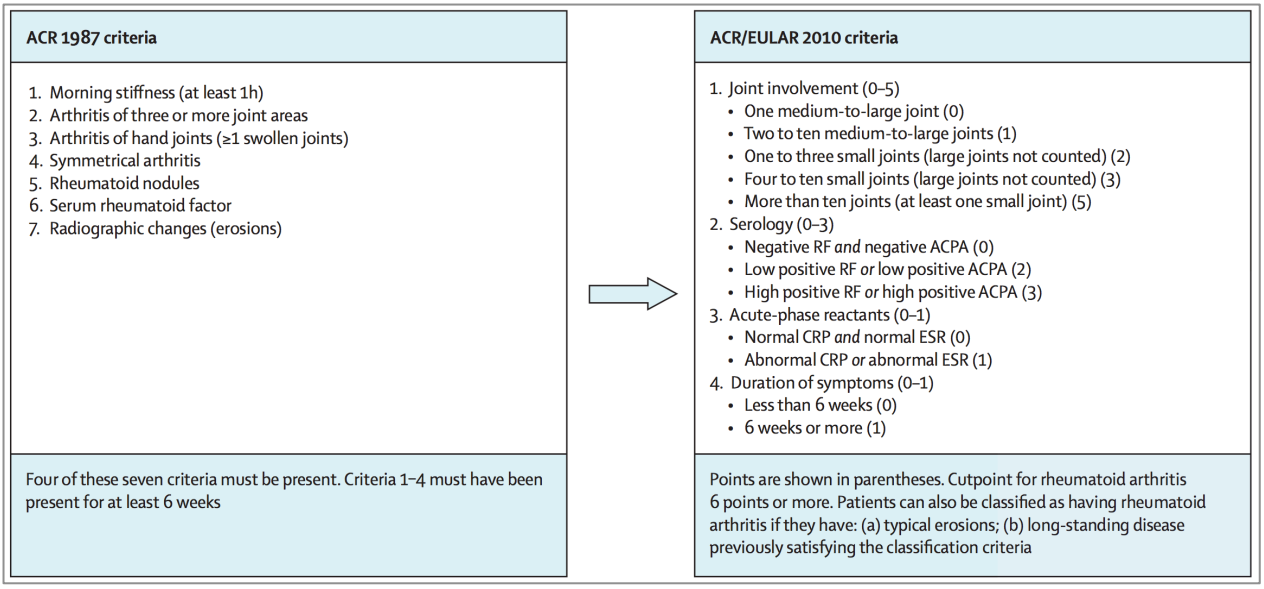


Figure 3. Conventional and new classification criteria for rheumatoid arthritis

Footnote: ACR 1987 criteria (left panel) were designed to classify established RA. 2010 ACR/EULAR criteria (right panel) are intended to classify both early and established disease.

Legend: ACR=American College of Rheumatology, EULAR=European League Against Rheumatism, RF=rheumatoid factor, ACPA=antibodies against citrullinated antigens, CRP=C-reactive protein, ESR=erythrocyte sedimentation rate.

Figure adapted from: Scott DL, Wolfe F, Huizinga TW. Rheumatoid arthritis. Lancet 2010;376(9746):1094-108.[10]

Treatment

No cure is currently available for RA. However, modern therapeutic approaches have allowed that increasing proportions of patients achieve satisfactory or excellent disease control. Current pharmacological treatment is based on the use of disease-modifying antirheumatic drugs (DMARDs). Therapeutic agents are considered DMARDs if they are, demonstrably, capable of inhibiting or halting progression of structural damage, as measured by radiographic scores, in addition to alleviating symptoms and signs of RA. Some treatments, such as nonsteroidal anti-inflammatory drugs (NSAIDs) and analgesics alleviated symptoms, but do not prevent the progression of structural damage.[4, 5]

DMARDs are categorized into synthetic (small chemical molecules given orally) and biologic (proteins administered parentally) agents. Synthetic DMARDS are divided into: conventional, which have evolved empirically, without a specific biological target in mind, and the modern targeted synthetic DMARDs, which have been specifically developed to inhibit enzymes involved in cytokines production, such as Janus kinases.[4,5] Methotrexate, a conventional synthetic DMARD, is first-line therapy and should be prescribed at an optimal dose of up to 25 mg weekly and in combination with glucocorticoids.[5] These are considered anchor drugs.[39-41] Sulfasalazine and leflunomide are also widely used and included in treatment recommendations, in case of failure or contraindication to methotrexate.[42] Hydroxychloroquine or chloroquine are usually considered DMARDs, although their ability to

prevent structural damage accrual as isolated agents is highly controversial.[4] If classical synthetic DMARD fail, sequential application of targeted therapies, such as biologic agents (e.g., tumor necrosis factor [TNF] inhibitors) or Janus kinase inhibitors, typically in combination with methotrexate, are recommended and used with good results.[5] There are currently four different modes of action of biological DMARDs approved for RA: TNF inhibition, interleukin 6 receptor inhibition, T-cell co-stimulation blockade, and B-cell depletion.[3] DMARDs are sometimes combined, and several combinations have proven efficacious, such as methotrexate, sulfasalazine, and hydroxychloroquine, termed triple therapy.[10]

The treatment of RA should also consider the adverse event profiles of the medications and other conditions of the patient (e.g. multiple sclerosis, hepatitis B or C, or pregnancy).[4,10] Monitoring of adverse effects and management of comorbidities is very important as well.[10] Some EULAR recommendations address specifically the management of cardiovascular risk in patients with RA and other forms of inflammatory joint disorders[43] or the reporting, screening and prevention of selected comorbidities.[44] Surgical treatment, particularly joint replacement surgery, may be necessary to keep function when joints are too damaged.[10]

Last but not least, non-pharmacological strategies are essential for the management of patients with RA. Among the strategies with more evidence basis are patient education, exercise, joint protection, foot care, and psychological support.[45,46-51] All these strategies are best delivered through the collaboration between rheumatologists, nurses, therapists, psychologists, podiatrists, nutritionists, among others.[10 52,53] However, despite the existing evidence[47-49] and the reference to these non-pharmacological strategies in some treatment recommendations[43 54] their implementation are still far from common practice.[6 55] One of the possible reasons for this lower implementation is that it is assumed that achieving remission (or low inflammatory activity) will suffice to abrogate the impact of the disease upon the patient and optimally serve his/her interests.[56 57] Another explanation for the greater (or exclusive) attention to pharmacological treatment may be that the tools used to assess remission are based mostly in physician's objective assessments.[58]

Current management strategies

An impressive improvement in the outcomes of patients with RA took place over the past two decades. This was possible not only due to the development of novel and more efficient DMARDs but, to a great extent, due to a serious of relevant paradigm shifts. Contrary to previous approaches, current treatment strategies strive for early referral, early diagnosis, early start of effective therapy, tight control of disease activity and consistent pursual of a

treatment target characterized by the absence of significant inflammatory activity.[54] The treatment should also be aimed at achieving remission or, at the least, low disease activity, as early and as consistently as possible. If treatment target is not reached medication should be changed without delay.[42 59-61] These treatment paradigms, epitomized by the Treat-to-Target strategy[62] is based on sound evidence that these guiding principles provide the best possible certainty of reducing or halting the progression of joint damage and disability.[63]

Essential for this strategy is the systematic use of reliable instruments to assess the degree of disease activity, and, thus, whether the treatment target has been achieved or a change in medication is warranted.[62]

The use of radiographic damage indices

One of the key treatment aims in RA is to prevent or halt structural changes and thereby minimize or reverse physical disability. X-ray images of hands (including wrists) and feet are therefore used to define if a therapeutic agent is DMARDs.[64,65] For this reason, this is an essential outcome in clinical trials, using very accurate and sensitive scoring methods.[65-67] The assessment of radiographic damage progression constitutes also an essential outcome to define rigorous criteria of remission because the structural stability is the major objective of remission as treatment target.[68] In routine practice, radiographs are usually done annually and evaluated semi-quantitatively only because radiographic damage is not used to make treatment decisions. These decisions are based on clinical and biological measures of disease activity,[58-60] described below.

Relevant clinical and biological measures of disease activity and target definition

The sections below revise concepts that are core to the work described in the thesis. We have, therefore, decided to focus this review on the state-of-the-art at the start of the work described herein, so as to convey a more precise description of the learning and research process that the thesis is supposed to describe.

A core set of clinical measures to assess RA was proposed decades ago by the American College of Rheumatology to be used in clinical trials.[69 70] It included three visual analogue scales (VAS) (the physician/observer and the patient global assessment of disease activity and the patient perception of pain), two joint counts (the number of tender joints and the number of swollen joints in a total of 28), one laboratory measure (ESR or CRP), a measure of function (usually the Health Assessment Questionnaire, HAQ)[71 72] and a measure for radiographic damage (in the case of trials of at least 1-year duration). These measures were

widely adopted by the scientific community but scarcely employed, if at all, in clinical practice.

Part of the revolution operated in the management of RA was the development and dissemination of easier to composite measures of disease activity, which include (in different weights) part of the individual components proposed by the ACR (Figure 4). These instruments allow a better characterization of disease activity as a continuous variable and provide cut-offs to define response criteria and remission, thus allowing tight control and regular check of whether target has or not been achieved.[62 73 74]

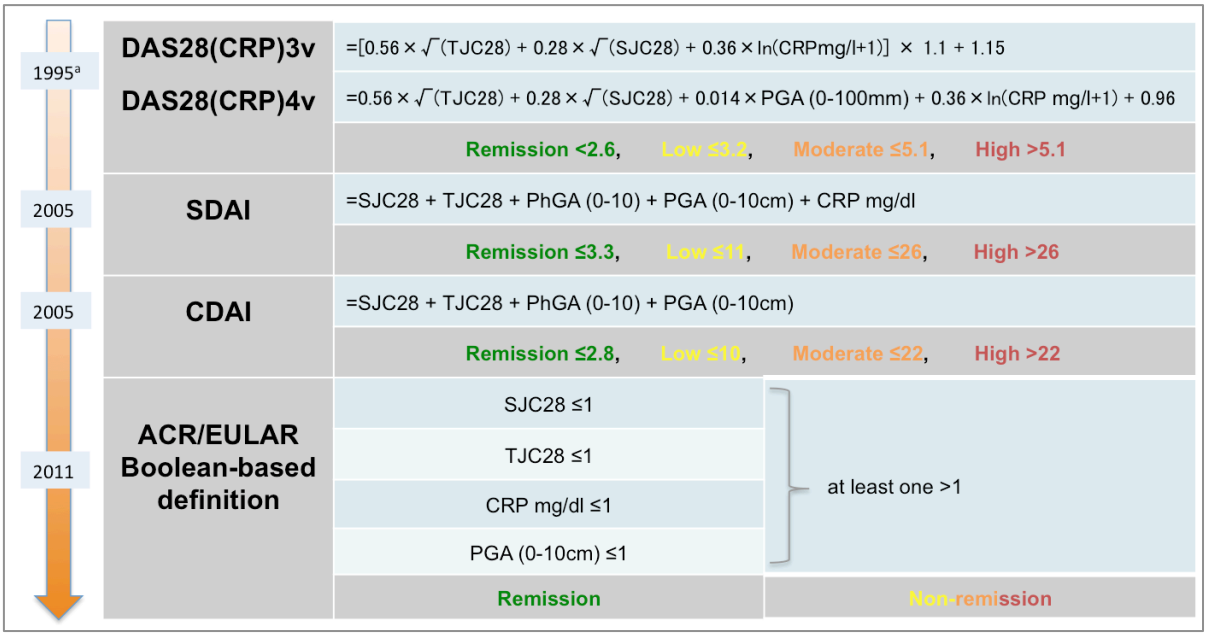


Figure 4. Disease activity measures used in rheumatoid arthritis

Figure footnote: This shows the components and scoring algorithms of four disease activity tools currently in use in clinical practice and in clinical trials in rheumatoid arthritis. They are presented in chronologic order of development. a. Although the DAS with 28-joint counts was developed in 1995, its original form with 68/66-joint counts was developed in early 1980s

Legend: CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; DAS, Disease Activity Score; ln, natural logarithm; PGA, Patient Global Assessment; PhGA, Physician Global Assessment; SDAI, Simplified Disease Activity Index; SJC28, swollen 28-joint count; TJC28, tender 28-joint count.

Source: the authors.

The use of these clinical assessment tools demonstrated good correlation with progression of damage and disability.[3 62 63 75] Among all available indices, the CDAI is most easy to perform, as it is a simple numerical summation of four variables.[76] The ACR/EULAR Boolean-based definition is the strictest, i.e. the most difficult to achieve definition of remission.[77] Despite being the most commonly used in practice, proposed cut-offs of the DAS28 are not supported by the most recent treatment recommendations[42 59] or by the internationally consensualised provisional definition of remission[68] as an adequate target to

guide the treatment strategy. This is due to its rather poor association with progression of joint damage,[77 78] Recently, the DAS28 cut-offs proposed to define remission were made stricter[79 80] but still the DAS28 was excluded from the currently proposed definition of remission.[68]

The relevance of patient-reported outcomes in the treatment and management of RA

RA impacts patient's lives in a variety of dimensions that are not captured by objective measures of disease activity. This holds true and important although it has been shown that current T2T strategy results in significant improvement of the impact of disease.[81 82]

A large number of validated PROs are available to measure a diversity of dimensions of RA from the patients perspective, including function (e.g. Health Assessment Questionnaire, HAQ),[71 72] Fatigue (e.g. Bristol Rheumatoid Arthritis Fatigue, BRAF),[83] Quality of Life (The Rheumatoid Arthritis Quality of Life Questionnaire, RAQoL),[84 85] Sleep (Athens Insomnia Scale, AIS)[86] among many others. These are frequently used in clinical trials and other research settings but not as routine clinical practice.

The definitions of remission, i.e. the ideal target of treatment, currently supported by ACR and EULAR integrate PGA.[64] This inclusion reflects the intention of considering the patient's perspective in treatment decisions, even if this is the only PRO taken into account.[87]

PGA is scored in a horizontal visual analogue scale of 10 cm. In the most commonly used formulation, the question is expressed as ""Considering all the ways your arthritis has affected you, how do you feel your arthritis is today?", with two anchors: "0=Inactive" and "10/100=Very active".[68] There a few variants of this formulations, as will be debated below.

The relative importance of PGA in the combined indices of disease activity has increased significantly over time (Figure 4): from a nearly irrelevant weight, to having the same impact in the final score as each of the clinical components in the ACR/EULAR Boolean-based definition of remission.[64] According to this guidance, a patient is considered in remission if all of the following four variables are ≤1: TJC28, SJC28, CRP (mg/dL) and PGA (0-10).[68]

PGA was selected for inclusion in the definition of remission because it is related with the rate of radiographic progression,[68] it is simple to use and is expected to conveys a global perspective of disease impact, as opposed to a large variety of other PROMs, which only measure specific dimensions, such as fatigue, sleep or function using rather extensive questionnaires. However, this decision was not without controversy, given that the relationship between PGA and actual disease activity had been questioned for a long time.[88 89] Concerns were also voiced regarding its poor standardization[90], its multiple

interpretations[91] and its susceptibility to influence by factors such as level of education, cultural background, comorbidity and psychological profile.[92 93] Despite this, PGA had become a crucial factor in the leading paradigm of treating to target.

Soon after this ACR/EULAR publication, Studenic and colleagues[94] and Veermer and colleagues,[95] almost at same time, published their studies on the effects of including PGA in these definitions in Austria and The Netherlands, respectively. The terminology "near-misses" was used for the first time in this context, to represent the patients that failed to reach remission due solely to one of the variables being >1.[94] In the first study, PGA was responsible for 61% of such cases, with SJC28 being the second highest "near-miss" with 20%.[94] The persistently high PGA was, in most cases, due to pain. In this study, it was pointed out that the physician's global assessment was ≤1 in 67% of the patients not fulfilling the PGA criterion, thus highlighting the frequent disagreement between patients and physicians in this respect.[94] In the study of Vermeer et al.,[95] 68% of the near-misses cases were due to PGA, consistent with the other study. Based on the data presented in both papers, we calculated that the proportion of all RA patients included that failed remission solely due to PGA was 31.3%[94] and 21.1%.[95] This demonstrated that a significant proportion of RA patients describe the persistence of significant impact of disease even after (almost) complete abrogation of the inflammatory process.

These patients in PGA-near -remission requires special attention , because they were exposed to the risk of overtreatment with immunosuppressive drugs when inflammation was already dully controlled , and missing interventions that might mitigate their persisting symptoms and improve quality of life.

Optimizing the delivery of person-centred care: The role of nurses

The wide range of consequences of RA requires life-long holistic management by a multidisciplinary team,[53] with a continuous need for adaptations addressing the contemporary unmet needs of these patients.[6]

The opportunities provided by PROMs to enhance the valorization of patient's perspective were well accepted,[96] but their implementation in practice is scarce in vast parts of the world. A variety of barriers have been identified. Probably the main one resides in the lack of adherence of healthcare professionals, who already face high workloads and short time slots for each consultation.[96] This makes it difficult to apply PROMs and interpret their scores, to focus and explore the patient's needs, and, on top of this, to make informed clinical

decisions.[97-99] Patients do value PROMs but these can only improve care if clinicians prioritise and use them.[98] The use of modern technologies certainly creates new opportunities, but we believe they will not suffice to solve the problem.

The most promising solution, according to the experience of leading centres, resides in expanding the involvement of other health professionals in the care of the patients with RA, with emphasis on nurses. Nurses already spend more time with patients than doctors in many health care settings,[100] and they are in a special position to foster the person-centered care because this is very close to the driving philosophy, ethics and core training of the profession.

The traditional role of the rheumatology nurse has evolved tremendously over the past three decades,[101,102-105] mainly due to the increasing volume and quality of research, fostered by the development of new treatment regimens for RA, organizational developments, and the increasing nursing education in many contexts, with possibilities of advanced degrees and specialization in some.[106]

However and despite of all the different interventions that nurses can perform for patients with RA,[107] the specific roles played by rheumatology nurses is still very limited in less advanced countries, including Portugal. [108 109] This is related to a number of factors, including education and training requirements and opportunities, cultural definitions, lack of tradition of inter-professional cooperation, limited human resources and policies of their government bodies and scientific-professional societies, among others. [109]

Every country needs to establish and define the role of the nurse in patients with a RA, but we believe that defining operational models for harmonious cooperation within multi-professional teams, can play an important role in fostering the dissemination of effective Person-centered care, PROMs and nurses are, most probably, indispensable key elements of such models.

Driving concerns and hypothesis

A number of concerns emerging from clinical practice and scientific literature gave body and momentum to the design and launch of this PhD project.

The predominant one was represented by the mismatch between the physicians' and the patients' perspectives of the condition designated as Rheumatoid Arthritis.[110] Physicians adopting an evidence-based practice saw RA as a combination of swollen joints, ESR or CRP values, with some consideration to pain and X-rays, and occasional attention to other measures of disease impact. The physician's global assessment of disease activity, the SJC

and acute phase reactants were the recognised drivers of treatment decisions in practice.[110] For the patient, RA is about pain, inability to perform daily tasks, work or leisure activities, difficulties in sleeping, having sex, enjoying life, participating in family and social endeavours, and coping with the disease.[110 111] This was obvious from clinical practice but also had scientific support.

Previous work under the auspices of EULAR, had involved a large number of patients from several European countries in an effort to identify the main domains of RA impact upon patients' lives and assess their relative importance. The end result was the RA Impact of Disease (RAID) score,[112 113] which includes seven domains, each assessed by a numeric rating scale and weighted to provide a final score: pain (21%), functional disability (16%), fatigue (15%), emotional well-being (12%), sleep (12%), coping (12%), and physical well-being (12%). Another important piece of evidence was provided by work to support the WHO's International Classification of Functioning, Disability and Health. In trying to identify the domains relevant to RA, a group of medical experts highlighted 76 dimensions of body functions and structures, activities/participation and environmental factors.[114] In a subsequent similar effort, patients with RA confirmed 74 of those dimensions and added an additional 66 items.[115]

Such observations, together with ethical imperatives, provided the main inspiration to this thesis: the need to enhance the impact of the patient's perspective upon the treatment decisions being taken on his behalf.

Inherent to this objective is the need to assess the validity and usefulness of the measures selected to represent the patients' perspective in the treatment decision process. Care would need to be taken to separately analyse this validity and usefulness at the group level (good for research purposes) and individual level (indispensable for clinical practice). Work initially predicted to be performed as part of this thesis, namely on the use of a new variant of RAID as a "tableau de bord" to guide person-centred care in RA was abandoned during the course of the project because it exceeded what was possible within this project. It is now the object of two additional PhD thesis.

A second major source of concern was represented by the notion that the strict adherence to established treatment recommendation would put patients in near-remission due to PGA at risk of unjustifiable overtreatment.

Addressing this issue would require evaluation of the prevalence of this problem in different settings and raise a rather daunting task: revisiting and questioning the provisional definitions of remission endorsed by ACR and EULAR. This could only be made if we could demonstrate that PGA was not an appropriate measure to be used as guidance to

immunosuppressive therapy and also that excluding PGA from the definition did not have a significant impact on its ability to predict radiographic progression. The hypothesis that we considered, from the start, a possible proposal of the exclusion of PGA from the driving treatment target, imposed the need to consider an alternative way to ensure that the perspective was not ignored but, rather, reinforced.

The third line of considerations referred to the constraints faced by health system in guaranteeing that physicians in charge of RA patients have the skills, the knowledge and, above all, the time to evaluate and manage patients concerns, beyond disease control. This called for an exploration of opportunities to reorganize the delivery of care considering multi-professional work teams. An enhanced role for nurses appeared as a plausible solution.

Thesis' Aims

The work presented in this thesis was intentionally designed to address the driving power and the quality of the representation of patient's perspective in current treatment paradigms of RA, epitomized by the T2T strategy. As work progressed, the work plan became focused on the validity of PGA's inclusion in the definition of remission (given its decisive impact) and on the need for an appropriate substitute. On ethical and technical grounds, we advocated, a priori, that the patients' experience of the disease (illness) merits a decisive weight in therapeutic decisions, given that the patient's interests and needs must be at the core of objectives of treatment (Person-centered care). In pursuing this aim we addressed six specific objectives:

1. To investigate the potential fragilities of PGA related to its lack of standardization and the need for patient's education on its scoring and intended use
2. To determine the influence of PGA on the proportion of patients achieving ACR/EULAR 2011 Boolean-based remission, exploring differences across countries
3. To understand the association of PGA with measures of disease activity, psychological/personality domains, comorbidities and other measures of disease impact, and whether correlates vary in different Boolean remission states (i.e. in 4v-remission, PGA-near-remission, and non-remission)
4. To clarify the longitudinal relationship of PGA with physical function and radiographic damage progression
5. To explore the potential value of considering separate targets to guide process-centered immunosuppressive therapy and person-centred adjunctive interventions
6. To design and propose a model of multi-professional team articulation aimed at optimized person-centered outcomes

REFERENCES

1. Myasoedova E, Crowson CS, Kremers HM, et al. Is the incidence of rheumatoid arthritis rising?: results from Olmsted County, Minnesota, 1955-2007. Arthritis Rheum 2010;62(6):1576-82.

2. Tobon GJ, Youinou P, Saraux A. The environment, geo-epidemiology, and autoimmune disease: Rheumatoid arthritis. J Autoimmun 2010;35(1):10-4.

3. Smolen JS, Aletaha D, Barton A, et al. Rheumatoid arthritis. Nat Rev Dis Primers 2018;4:18001.

4. Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. Lancet 2016;388(10055):2023-38.

5. Aletaha D, Smolen JS. Diagnosis and Management of Rheumatoid Arthritis: A Review. JAMA 2018;320(13):1360-72.

6. Taylor PC, Moore A, Vasilescu R, et al. A structured literature review of the burden of illness and unmet needs in patients with rheumatoid arthritis: a current perspective. Rheumatol Int 2016;36(5):685-95.

7. Sokka T, Kautiainen H, Pincus T, et al. Work disability remains a major problem in rheumatoid arthritis in the 2000s: data from 32 countries in the QUEST-RA study. Arthritis Res Ther 2010;12(2):R42.

8. Silman AJ, Pearson JE. Epidemiology and genetics of rheumatoid arthritis. Arthritis Res 2002;4 Suppl 3:S265-72.

9. Alamanos Y, Voulgari PV, Drosos AA. Incidence and prevalence of rheumatoid arthritis, based on the 1987 American College of Rheumatology criteria: a systematic review. Semin Arthritis Rheum 2006;36(3):182-8.

10. Scott DL, Wolfe F, Huizinga TW. Rheumatoid arthritis. Lancet 2010;376(9746):1094-108.

11. Symmons D, Turner G, Webb R, et al. The prevalence of rheumatoid arthritis in the United Kingdom: new estimates for a new century. Rheumatology (Oxford) 2002;41(7):793-800.

12. Branco JC, Rodrigues AM, Gouveia N, et al. Prevalence of rheumatic and musculoskeletal diseases and their impact on health-related quality of life, physical function and mental health in Portugal: results from EpiReumaPt- a national health survey. RMD Open 2016;2(1):e000166.

13. Smolen JS, Steiner G. Therapeutic strategies for rheumatoid arthritis. Nat Rev Drug Discov 2003;2(6):473-88.

14. Sugiyama D, Nishimura K, Tamaki K, et al. Impact of smoking as a risk factor for developing rheumatoid arthritis: a meta-analysis of observational studies. Ann Rheum Dis 2010;69(1):70-81.

15. Hayer S, Bauer G, Willburger M, et al. Cartilage damage and bone erosion are more prominent determinants of functional impairment in longstanding experimental arthritis than synovial inflammation. Dis Model Mech 2016;9(11):1329-38.

16. Welsing PM, van Gestel AM, Swinkels HL, et al. The relationship between disease activity, joint destruction, and functional capacity over the course of rheumatoid arthritis. Arthritis Rheum 2001;44(9):2009-17.

17. Young A, Koduri G. Extra-articular manifestations and complications of rheumatoid arthritis. Best Pract Res Clin Rheumatol 2007;21(5):907-27.

18. Bartels C, Bell C, Rosenthal A, et al. Decline in rheumatoid vasculitis prevalence among US veterans: a retrospective cross-sectional study. Arthritis Rheum 2009;60(9):2553-7.

19. Crowson CS, Rollefstad S, Ikdahl E, et al. Impact of risk factors associated with cardiovascular outcomes in patients with rheumatoid arthritis. Ann Rheum Dis 2018;77(1):48-54.

20. Choi HK, Hernan MA, Seeger JD, et al. Methotrexate and mortality in patients with rheumatoid arthritis: a prospective study. Lancet 2002;359(9313):1173-7.

21. Jacobsson LT, Turesson C, Nilsson JA, et al. Treatment with TNF blockers and mortality risk in patients with rheumatoid arthritis. Ann Rheum Dis 2007;66(5):670-5.

22. Low AS, Symmons DP, Lunt M, et al. Relationship between exposure to tumour necrosis factor inhibitor therapy and incidence and severity of myocardial infarction in patients with rheumatoid arthritis. Ann Rheum Dis 2017;76(4):654-60.

23. Gist AC, Guymer EK, Eades LE, et al. Fibromyalgia remains a significant burden in rheumatoid arthritis patients in Australia. Int J Rheum Dis 2018;21(3):639-46.

24. Duffield SJ, Miller N, Zhao S, et al. Concomitant fibromyalgia complicating chronic inflammatory arthritis: a systematic review and meta-analysis. Rheumatology (Oxford) 2018;57(8):1453-60.

25. Matcham F, Scott IC, Rayner L, et al. The impact of rheumatoid arthritis on quality-of-life assessed using the SF-36: a systematic review and meta-analysis. Semin Arthritis Rheum 2014;44(2):123-30.

26. van Steenbergen HW, Tsonaka R, Huizinga TW, et al. Fatigue in rheumatoid arthritis; a persistent problem: a large longitudinal study. RMD Open 2015;1(1):e000041.

27. Radner H, Smolen JS, Aletaha D. Comorbidity affects all domains of physical function and quality of life in patients with rheumatoid arthritis. Rheumatology (Oxford) 2011;50(2):381-8.

28. Kobelt G, Lindgren P, Lindroth Y, et al. Modelling the effect of function and disease activity on costs and quality of life in rheumatoid arthritis. Rheumatology (Oxford) 2005;44(9):1169-75.

29. Bansback N, Marra CA, Finckh A, et al. The economics of treatment in early rheumatoid arthritis. Best Pract Res Clin Rheumatol 2009;23(1):83-92.

30. Lundkvist J, Kastang F, Kobelt G. The burden of rheumatoid arthritis and access to treatment: health burden and costs. Eur J Health Econ 2008;8 Suppl 2:S49-60.

31. Levy L, Fautrel B, Barnetche T, et al. Incidence and risk of fatal myocardial infarction and stroke events in rheumatoid arthritis patients. A systematic review of the literature. Clin Exp Rheumatol 2008;26(4):673-9.

32. Mehta B, Pedro S, Ozen G, et al. Serious infection risk in rheumatoid arthritis compared with non-inflammatory rheumatic and musculoskeletal diseases: a US national cohort study. RMD Open 2019;5(1):e000935.

33. Yun H, Xie F, Delzell E, et al. Comparative Risk of Hospitalized Infection Associated With Biologic Agents in Rheumatoid Arthritis Patients Enrolled in Medicare. Arthritis Rheumatol 2016;68(1):56-66.

34. Sparks JA, Chang SC, Liao KP, et al. Rheumatoid Arthritis and Mortality Among Women During 36 Years of Prospective Follow-Up: Results From the Nurses' Health Study. Arthritis Care Res (Hoboken) 2016;68(6):753-62.

35. Markusse IM, Akdemir G, Dirven L, et al. Long-Term Outcomes of Patients With Recent-Onset Rheumatoid Arthritis After 10 Years of Tight Controlled Treatment: A Randomized Trial. Ann Intern Med 2016;164(8):523-31.

36. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31(3):315-24.

37. Banal F, Dougados M, Combescure C, et al. Sensitivity and specificity of the American College of Rheumatology 1987 criteria for the diagnosis of rheumatoid arthritis according to disease duration: a systematic literature review and meta-analysis. Ann Rheum Dis 2009;68(7):1184-91.

38. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010;62(9):2569-81.

39. Bijlsma JW, Jacobs JW. Methotrexate: still the anchor drug in RA treatment. Joint Bone Spine 2009;76(5):452-4.

40. van der Goes MC, Jacobs JW, Bijlsma JW. The value of glucocorticoid co-therapy in different rheumatic diseases--positive and adverse effects. Arthritis Res Ther 2014;16 Suppl 2(Suppl 2):S2-S2.

41. Favalli EG, Biggioggero M, Meroni PL. Methotrexate for the treatment of rheumatoid arthritis in the biologic era: still an "anchor" drug? Autoimmun Rev 2014;13(11):1102-8.

42. Smolen JS, Landewe R, Bijlsma J, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis 2017;76(6):960-77.

43. Agca R, Heslinga SC, Rollefstad S, et al. EULAR recommendations for cardiovascular disease risk management in patients with rheumatoid arthritis and other forms of inflammatory joint disorders: 2015/2016 update. Ann Rheum Dis 2017;76(1):17-28.

44. Baillet A, Gossec L, Carmona L, et al. Points to consider for reporting, screening for and preventing selected comorbidities in chronic inflammatory rheumatic diseases in daily practice: a EULAR initiative. Ann Rheum Dis 2016;75(6):965-73.

45. Christie A, Jamtvedt G, Dahm KT, et al. Effectiveness of nonpharmacological and nonsurgical interventions for patients with rheumatoid arthritis: an overview of systematic reviews. Phys Ther 2007;87(12):1697-715.

46. Santos EJF, Duarte C, Marques A, et al. Effectiveness of non-pharmacological and non-surgical interventions for rheumatoid arthritis: an umbrella review. JBI Database System Rev Implement Rep 2019;17(7):1494-531.

47. Rausch Osthoff AK, Niedermann K, Braun J, et al. 2018 EULAR recommendations for physical activity in people with inflammatory arthritis and osteoarthritis. Ann Rheum Dis 2018;77(9):1251-60.

48. Geenen R, Overman CL, Christensen R, et al. EULAR recommendations for the health professional's approach to pain management in inflammatory arthritis and osteoarthritis. Ann Rheum Dis 2018;77(6):797-807.

49. Zangi HA, Ndosi M, Adams J, et al. EULAR recommendations for patient education for people with inflammatory arthritis. Ann Rheum Dis 2015;74(6):954-62.

50. Cramp F, Hewlett S, Almeida C, et al. Non-pharmacological interventions for fatigue in rheumatoid arthritis. Cochrane Database Syst Rev 2013(8):Cd008322.

51. Hewlett S, Almeida C, Ambler N, et al. Reducing arthritis fatigue impact: two-year randomised controlled trial of cognitive behavioural approaches by rheumatology teams (RAFT). Ann Rheum Dis 2019;78(4):465-72.

52. Vliet Vlieland TP. Multidisciplinary team care and outcomes in rheumatoid arthritis. Curr Opin Rheumatol 2004;16.

53. Kiely PDW, Nikiphorou E. Management of rheumatoid arthritis. Medicine (Baltimore) 2018;46(4):216-21.

54. Combe B, Landewe R, Daien CI, et al. 2016 update of the EULAR recommendations for the management of early arthritis. Ann Rheum Dis 2017;76(6):948-59.

55. Esselens G, Westhovens R, Verschueren P. Effectiveness of an integrated outpatient care programme compared with present-day standard care in early rheumatoid arthritis. Musculoskeletal Care 2009;7(1):1-16.

56. Strand V, Singh JA. Newer biological agents in rheumatoid arthritis: impact on health-related quality of life and productivity. Drugs 2010;70(2):121-45.

57. Chen JS, Makovey J, Lassere M, et al. Comparative effectiveness of anti-tumor necrosis factor drugs on health-related quality of life among patients with inflammatory arthritis. Arthritis Care Res (Hoboken) 2014;66(3):464-72.

58. Gul HL, Ferreira JF, Emery P. Remission in rheumatoid arthritis: is it all the same? Expert Review of Clinical Pharmacology 2015;8(5):575-86.

59. Singh JA, Saag KG, Bridges SL, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Care Res 2016;68(1):1-25.

60. Duarte AC, Santos-Faria D, Goncalves MJ, et al. Portuguese recommendations for the use of methotrexate in rheumatic diseases - 2016 update. Acta Reumatol Port 2017;42(2):127-40.

61. Duarte C, Sousa-Neves J, Agueda A, et al. Portuguese Recommendations for the use of biological therapies in patients with rheumatoid arthritis- 2016 update. Acta Reumatol Port 2017;42(2)(Apr-Jun):112-26.

62. Smolen JS, Breedveld FC, Burmester GR, et al. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. Ann Rheum Dis 2015;75(1):3-15.

63. Stoffer MA, Schoels MM, Smolen JS, et al. Evidence for treating rheumatoid arthritis to target: results of a systematic literature search update. Ann Rheum Dis 2016;75(1):16-22.

64. Felson DT, Smolen JS, Wells G, et al. American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Arthritis Rheum 2011;63(3):573-86.

65. Ory PA. Interpreting radiographic data in rheumatoid arthritis. Ann Rheum Dis 2003;62(7):597-604.

66. Navarro-Compan V, Gherghe AM, Smolen JS, et al. Relationship between disease activity indices and their individual components and radiographic progression in RA: a systematic literature review. Rheumatology (Oxford) 2015;54(6):994-1007.

67. van der Heijde D. Structural damage in rheumatoid arthritis as visualized through radiographs. Arthritis Res 2002;4 Suppl 2:S29-33.

68. Felson DT, Smolen JS, Wells G, et al. American College of Rheumatology/European League against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Ann Rheum Dis 2011;70(3):404-13.

69. Felson DT, Anderson JJ, Boers M, et al. The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. The Committee on Outcome Measures in Rheumatoid Arthritis Clinical Trials. Arthritis Rheum 1993;36(6):729-40.

70. Castrejon I, Pincus T. Patient self-report outcomes to guide a treat-to-target strategy in clinical trials and usual clinical care of rheumatoid arthritis. Clin Exp Rheumatol 2012;30(4 Suppl 73):S50-5.

71. Fries JF, Spitz P, Kraines RG, et al. Measurement of patient outcome in arthritis. Arthritis Rheum 1980;23(2):137-45.

72. Bruce B, Fries JF. The Health Assessment Questionnaire (HAQ). Clin Exp Rheumatol 2005;23(5 Suppl 39):S14-8.

73. Smolen JS, Aletaha D. Monitoring rheumatoid arthritis. Curr Opin Rheumatol 2011;23(3):252-8.

74. Smolen JS, Aletaha D, Bijlsma JW, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. Ann Rheum Dis 2010;69(4):631-7.

75. Smolen JS, Han C, van der Heijde DM, et al. Radiographic changes in rheumatoid arthritis patients attaining different disease activity states with methotrexate monotherapy and infliximab plus methotrexate: the impacts of remission and tumour necrosis factor blockade. Ann Rheum Dis 2009;68(6):823-7.

76. Aletaha D, Smolen J. The Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI): a review of their usefulness and validity in rheumatoid arthritis. Clin Exp Rheumatol 2005;23(5 Suppl 39):S100-8.

77. Bykerk VP, Massarotti EM. The new ACR/EULAR remission criteria: rationale for developing new criteria for remission. Rheumatology (Oxford) 2012;51(suppl_6):vi16-vi20.

78. Boers M. Let's stop fooling ourselves. In RA, only ACR/EULAR criteria define remission and equate with absence of disease! Ann Rheum Dis 2016;75(10):e68.

79. Fleischmann R, van der Heijde D, Koenig AS, et al. How much does Disease Activity Score in 28 joints ESR and CRP calculations underestimate disease activity compared with the Simplified Disease Activity Index? Ann Rheum Dis 2015;74(6):1132-7.

80. Fleischmann RM, van der Heijde D, Gardiner PV, et al. DAS28-CRP and DAS28-ESR cut-offs for high disease activity in rheumatoid arthritis are not interchangeable. RMD Open 2017;3(1):e000382.

81. Kekow J, Moots R, Khandker R, et al. Improvements in patient-reported outcomes, symptoms of depression and anxiety, and their association with clinical remission among patients with moderate-to-severe active early rheumatoid arthritis. Rheumatology (Oxford) 2011;50(2):401-9.

82. Radner H, Smolen JS, Aletaha D. Remission in rheumatoid arthritis: benefit over low disease activity in patient-reported outcomes and costs. Arthritis Res Ther 2014;16(1):R56.

83. Hewlett S, Dures E, Almeida C. Measures of fatigue: Bristol Rheumatoid Arthritis Fatigue Multi-Dimensional Questionnaire (BRAF MDQ), Bristol Rheumatoid Arthritis Fatigue Numerical Rating Scales (BRAF NRS) for severity, effect, and coping, Chalder Fatigue Questionnaire (CFQ), Checklist Individual Strength (CIS20R and CIS8R), Fatigue Severity Scale (FSS), Functional Assessment Chronic Illness Therapy (Fatigue) (FACIT-F), Multi-Dimensional Assessment of Fatigue (MAF), Multi-Dimensional Fatigue Inventory (MFI), Pediatric Quality Of Life (PedsQL) Multi-Dimensional Fatigue Scale, Profile of Fatigue (ProF), Short Form 36 Vitality Subscale (SF-36 VT), and Visual Analog Scales (VAS). Arthritis Care Res (Hoboken) 2011;63 Suppl 11:S263-86.

84. de Jong Z, van der Heijde D, McKenna SP, et al. The reliability and construct validity of the RAQoL: a rheumatoid arthritis-specific quality of life instrument. Br J Rheumatol 1997;36(8):878-83.

85. Duarte C, Fernandes F, Madeira N, et al. Validation of Rheumatoid Arthritis Quality of Life (RAQoL) Questionnaire into Portuguese Language. Acta Reumatol Port 2019;44(1):65-70.

86. Wells GA, Li T, Kirwan JR, et al. Assessing quality of sleep in patients with rheumatoid arthritis. J Rheumatol 2009;36(9):2077-86.

87. van Tuyl LH, Smolen JS, Wells GA, et al. Patient perspective on remission in rheumatoid arthritis. J Rheumatol 2011;38(8):1735-8.

88. Nicolau G, Yogui MM, Vallochi TL, et al. Sources of discrepancy in patient and physician global assessments of rheumatoid arthritis disease activity. J Rheumatol 2004;31(7):1293-6.

89. Neogi T, Xie H, Felson DT. Relative responsiveness of physician/assessor-derived and patient-derived core set measures in rheumatoid arthritis trials. J Rheumatol 2008;35(5):757-62.

90. French T, Hewlett S, Kirwan J, et al. Different wording of the patient global visual analogue scale (PG-VAS) affects rheumatoid arthritis patients' scoring and the overall disease activity score (DAS28): a cross-sectional study. Musculoskeletal Care 2013;11(4):229-37.

91. van Tuyl LH, Boers M. Patient's global assessment of disease activity: what are we measuring? Arthritis Rheum 2012;64(9):2811-3.

92. Masri KR, Shaver TS, Shahouri SH, et al. Validity and reliability problems with patient global as a component of the ACR/EULAR remission criteria as used in clinical practice. J Rheumatol 2012;39(6):1139-45.

93. Inanc N, Yilmaz-Oner S, Can M, et al. The role of depression, anxiety, fatigue, and fibromyalgia on the evaluation of the remission status in patients with rheumatoid arthritis. J Rheumatol 2014;41(9):1755-60.

94. Studenic P, Smolen JS, Aletaha D. Near misses of ACR/EULAR criteria for remission: effects of patient global assessment in Boolean and index-based definitions. Ann Rheum Dis 2012;71(10):1702-5.

95. Vermeer M, Kuper HH, van der Bijl AE, et al. The provisional ACR/EULAR definition of remission in RA: a comment on the patient global assessment criterion. Rheumatology (Oxford) 2012;51(6):1076-80.

96. Fautrel B, Alten R, Kirkham B, et al. Call for action: how to improve use of patient-reported outcomes to guide clinical decision making in rheumatoid arthritis. Rheumatol Int 2018;38(6):935-47.

97. Porter I, Goncalves-Bradley D, Ricci-Cabello I, et al. Framework and guidance for implementing patient-reported outcomes in clinical practice: evidence, challenges and opportunities. J Comp Eff Res 2016;5(5):507-19.

98. Talib TL, DeChant P, Kean J, et al. A qualitative study of patients' perceptions of the utility of patient-reported outcome measures of symptoms in primary care clinics. Qual Life Res 2018;27(12):3157-66.

99. Ganesan N. Adopting Patient-Reported Outcomes in Clinical Care: Challenges and Opportunities. Washington: Avalere, 2018:15.

100. Cottrell JE, Jonas M, Bergsten U, et al. The Nurse's Role in Addressing Unmet Treatment and Management Needs of Patients With Rheumatoid Arthritis: Delphi-Based Recommendations. Int J Nurs Knowl 2012.

101. Hill J, Bird HA, Harmer R, et al. An evaluation of the effectiveness, safety and acceptability of a nurse practitioner in a rheumatology outpatient clinic. Br J Rheumatol 1994;33(3):283-8.

102. Hill J, Hale C. Clinical skills: evidence-based nursing care of people with rheumatoid arthritis. Br J Nurs 2004;13(14):852-7.

103. Ndosi M, Johnson D, Young T, et al. Effects of needs-based patient education on self-efficacy and health outcomes in people with rheumatoid arthritis: a multicentre, single blind, randomised controlled trial. Ann Rheum Dis 2015.

104. Ndosi M, Johnson D, Young T, et al. Effects of needs-based patient education on self-efficacy and health outcomes in people with rheumatoid arthritis: a multicentre, single blind, randomised controlled trial. Ann Rheum Dis 2016;75(6):1126-32.

105. Ndosi M, Vinall K, Hale C, et al. The effectiveness of nurse-led care in people with rheumatoid arthritis: a systematic review. Int J Nurs Stud 2011;48(5):642-54.

106. Oliver S, Leary A. The value of the nurse specialists' role: Pandora initial findings. Musculoskeletal Care 2010;8(3):175-7.

107. van Eijk-Hustings Y, van Tubergen A, Bostrom C, et al. EULAR recommendations for the role of the nurse in the management of chronic inflammatory arthritis. Ann Rheum Dis 2012;71(1):13-9.

108. Barbosa L, Ramiro S, Santos MJ, et al. Applicability of the EULAR recommendations on the role of the nurse in the management of chronic inflammatory arthritis in Portugal. Acta Reumatol Port 2013;38(3):186-91.

109. Vliet Vlieland TP, van den Ende CH, Alliot-Launois F, et al. Educational needs of health professionals working in rheumatology in Europe. RMD Open 2016;2(2):e000337.

110. Studenic P, Radner H, Smolen JS, et al. Discrepancies between patients and physicians in their perceptions of rheumatoid arthritis disease activity. Arthritis Rheum 2012;64(9):2814-23.

111. da Silva JA, Ramiro S, Pedro S, et al. Patients- and physicians- priorities for improvement. The case of rheumatic diseases. Acta Reumatol Port 2010;35(2):192-9.

112. Gossec L, Dougados M, Rincheval N, et al. Elaboration of the preliminary Rheumatoid Arthritis Impact of Disease (RAID) score: a EULAR initiative. Ann Rheum Dis 2009;68(11):1680-5.

113. Gossec L, Paternotte S, Aanerud GJ, et al. Finalisation and validation of the rheumatoid arthritis impact of disease score, a patient-derived composite measure of impact of rheumatoid arthritis: a EULAR initiative. Ann Rheum Dis 2011;70(6):935-42.

114. Stucki G, Cieza A, Geyh S, et al. ICF Core Sets for rheumatoid arthritis. J Rehabil Med 2004(44 Suppl):87-93.

115. Coenen M, Cieza A, Stamm TA, et al. Validation of the International Classification of Functioning, Disability and Health (ICF) Core Set for rheumatoid arthritis from the patient perspective using focus groups. Arthritis Res Ther 2006;8(4):R84.

Chapter II

THE IMPORTANCE OF PATIENT GLOBAL ASSESSMENT (PGA)'S STANDARDIZATION AND EDUCATION ABOUT ITS PURPOSE IN RA

This chapter includes 3 published manuscripts

Manuscript 1

Influence of the different "patient global assessment" formulations on disease activity score by different indices in rheumatoid arthritis.

Ferreira RJO*, Eugénio G*, Ndosi M, Silva C, Medeiros C, Duarte C, da Silva JAP

Clin Rheumatol. 2018; 37(7):1963-1969.

JOURNAL'S IMPACT FACTOR: 2.293

Number of external citations*: 3

Number of self-citations*: 1

CONFERENCES PRESENTATIONS/ABSTRACTS

Conference*:* Pfizer Summit 2015 (Évora). Poster presentation - **Award best poster**

- Here we presented the preliminary results (n=101)

Conference*:* EULAR Annual Congress 2017 (Madrid, Spain). Poster Presentation.

Abstract*:* Eugénio G, Ferreira RJO, Silva C, et al THU0145 Impact of different formulations of "patient global assessment" on remission classification by disease activity indices in rheumatoid arthritis (2017). *Ann Rheum Dis.* 76 (Suppl 2), 255-256.

- Here we presented the final results (n=193)

Journal's Impact Factor: 14.299

Number of external citations*: 0

Number of self-citations*: 0

OTHER SCIENTIFIC OUTPUTS

Thesis: Medeiros C. (2015). [PGA Rheumatoid arthritis: Formulation of the questions and correlation with DAS28]. Master in Medicine. Faculty of Medicine, University of Coimbra, Coimbra, Portugal. Available at http://hdl.handle.net/10316/30666

- This thesis presented the results obtained from data of the first 101 patients.

Visualizations*: 1405 (among the 5% most viewed)

Downloads*: 80 (among the 20% most downloaded)

* until 30th august 2019

Clinical Rheumatology
https://doi.org/10.1007/s10067-018-4063-9

BRIEF REPORT

Influence of the different "patient global assessment" formulations on disease activity score by different indices in rheumatoid arthritis

Ricardo J. O. Ferreira[1,2,3] · Gisela Eugénio[1] · Mwidimi Ndosi[4,5] · Cristiana Silva[6] · Catarina Medeiros[7] · Cátia Duarte[1,8] · J. A. P. da Silva[1,8]

Received: 1 February 2018 / Accepted: 1 March 2018

Abstract

Patient global assessment (PGA) is included in almost all rheumatoid arthritis (RA) composite disease activity indices and definitions of remission. However, different PGA formulations exist and are used interchangeably in research and clinical practice. We investigated how five different PGA formulations used in four disease indices affect the remission rates. This was an ancillary analysis of data from a cross-sectional study in patients with RA. The data comprised the following: 28-joint counts, C-reactive protein, and five PGA formulations. Remission rate variation was assessed using five PGA formulations in each index (ACR/EULAR Boolean, CDAI, SDAI, and DAS28-CRP). PGA agreement was assessed by the following: Pearson's correlation; Bland-Altman plots; paired samples *t* test; and establishing the proportion of patients who scored (i) all formulations within an interval of 20 mm and (ii) each formulation ≤ 10 mm. This analysis included 191 patients. PGA formulations presented good correlations (≥ 0.65), but Bland-Altman plots showed clinically significant differences, which were statistically confirmed by comparison of means. Just over a half (51.8%) of patients scored all PGA formulations within a 20-mm interval. The proportion of those scoring ≤ 10 mm varied from 11.5 to 16.2%. When different formulations of PGA were used in each index, remission differences of up to 4.7, 4.7, 6.3, and 5.2% were observed. When formulations were used in their respective indices, as validated, the remission rates were similar (13.1, 13.6, 14.1, and 18.3%). Using PGA formulations interchangeably may have implications in the assessment of disease activity and in the attainment of remission, and this can impact upon management decisions.

Keywords Disease activity · Patient global assessment · Patient preference · Patient reported outcome measures · Remission induction · Rheumatoid arthritis

Ricardo J. O. Ferreira and Gisela Eugénio contributed equally to this work.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10067-018-4063-9) contains supplementary material, which is available to authorized users.

✉ Ricardo J. O. Ferreira
ferreira.rjo@gmail.com

[1] Rheumatology Department, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal

[2] Health Sciences Research Unit: Nursing (UICiSA:E), Escola superior de Enfermagem de Coimbra, Coimbra, Portugal

[3] Serviço de Reumatologia, Consulta Externa, Piso 7, Centro Hospitalar Universitário de Coimbra, EPE, Avenida Dr Bissaya Barreto, 3000-075 Coimbra, Portugal

[4] Department of Nursing and Midwifery, University of the West of England, Bristol, UK

[5] Academic Rheumatology Unit, University Hospitals Bristol, Bristol, UK

[6] Faculty of Medicine, University of Coimbra, Coimbra, Portugal

[7] Internal Medicine Department, Centro Hospitalar Médio Tejo, Unidade de Abrantes, Torres Novas, Portugal

[8] Clínica Universitária de Reumatologia, Faculty of Medicine, University of Coimbra, Coimbra, Portugal

Published online: 10 March 2018

Introduction

In the last two decades, significant advances have been observed in the treatment of rheumatoid arthritis (RA) as a result not only of the introduction of new therapies but also of new strategies, such as "treat-to-target" (T2T) [1]. Remission or at least low disease activity (LDA) has become a consensual guiding target for therapy [2–4], as this provides the best assurance of good structural and functional outcomes [5]. Thus, the assessment of disease activity is crucial, and the use of combined indices and their cut-offs is recommended to guide and evaluate treatment options, both in research and in clinical practice [2–4].

However, a "gold standard" definition of remission has not been established [2]. The four commonly used definitions are as follows: Disease Activity Score 28 (DAS28)-based remission [4, 6], the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) Boolean-based remission, the Clinical Disease Activity Index (CDAI)-based remission, and the Simplified Disease Activity Index (SDAI)-based remission; the last two have been elected as preferential [2, 3]. Not surprisingly, different criteria provide different rates of remission [7].

Patient global assessment (PGA) is the only patient-reported outcome (PRO) included in all of the above-mentioned disease activity indices, and considerable attention has been paid recently to its influence on remission rates [8–10]. Several limitations have been pointed out to this assessment, including variations in the (i) phrasing of the question (e.g., "disease," "arthritis," or "health"), (ii) phrasing of the anchors (e.g., "very well" or "the best"), (iii) type of rating scale (e.g., visual analogue scale (VAS) with 10 cm or numeric rating scale (NRS) from 0 to 10), and (iv) time intervals to which the evaluation refers (e.g., "last week" or "today") [10, 11]. Despite these observations, the different formulations of PGA seem to be used indistinctly in both clinical practice and in research [10].

This study aimed at (i) evaluating if and how the score of PGA by patients with RA differs according to the formulation of the question and (ii) assessing the influence of this variability upon remission and LDA rates obtained with four different indices.

Participants and methods

Study design and setting

This was an ancillary analysis of data from an observational, cross-sectional study, performed in a single rheumatology outpatient department [9].

Participants

The original study included consecutive adult patients with a definite diagnosis of RA (ACR 1987 revised criteria or ACR/EULAR 2010 classification criteria). Patients were excluded if they declined participation or if they were unable to respond to the questionnaires unaided. Ethical approval was granted by the Ethics Committee of the Faculty of Medicine, University of Coimbra (CE-037/2015). All patients signed consent according to the Declaration of Helsinki. Additional consent for this ancillary study was not required. Here, data was included from patients who had completed the five versions of PGA and had information for all disease activity indices.

Patient global assessment

All patients assessed their PGA using the following different formulations:

- "Considering all the ways your arthritis has affected you, how do you feel your arthritis is today?" as recommended by ACR/EULAR [2] (v1).
- "Considering all the ways your arthritis affects you, rate how well you are doing on the following scale"—as in CDAI and SDAI [12] (v2)
- "How well do you consider your health status during the past week?"—as in the original DAS28 [13] (v3)
- "How active was your arthritis during the past week?"—as by current DAS28 [13] (v4)
- "Your disease has ups and downs. When it is very active ("alight," "scalded/hot"), there is more pain, morning stiffness, joint swelling and tiredness. Taking this into account, how would you rate the state of your disease over the last week?"—PGA formulated by investigators (v5).

All formulations were presented as a 0–100-mm, unmarked, horizontal VAS, with their respective anchors.

Other variables

Questionnaires included patient demographic data and other PROs, as described elsewhere [9]. The attending physician provided the following: tender 28-joint count (TJC28), swollen 28-joint count (SJC28), C-reactive protein (CRP), and Physician Global Assessment (PhGA).

Each formulation of PGA was presented in a single page of the questionnaire, interspersed with other PROs to serve as "distractors" [11], and these were completed before clinical consultations.

Disease activity indices

The following disease activity indices and respective cut-off points were used to assess remission: (i) ACR/EULAR Boolean-based definition of remission: TJC28, SJC28, CRP (in mg/dl), and PGA (in cm) all ≤ 1 [2], (ii) SDAI ≤ 3.3 [12], (iii) CDAI ≤ 2.8 [12], and (iv) DAS28-CRP < 1.9 [6]. Cut-offs for LDA state were as follows: SDAI ≤ 11 [12], CDAI ≤ 10 [12], and DAS28-CRP ≤ 3.1 [6].

Statistical methods

Differences across the five PGA formulations were assessed by the following: (i) Pearson's correlation coefficients; (ii) Bland-Altman plots (with limits of agreement of $1.96 \times SD_{mean\ difference}$) [14], using the ACR/EULAR formulation (v1) as the reference (defined a priori, based on results of a systematic review [10]); (iii) paired samples *t* test, comparing the mean scores obtained with each formulation, (v1 used as reference); (iv) examining the proportion of patients who scored all PGA formulations within an interval of 20 mm; (v) comparing the proportion of patients who scored each formulation ≤ 10 mm; and (vi) comparing the proportion of patients classified as in remission (and in LDA) according to each formulation; chi-square test was used to test this difference, namely using indices with their assigned PGA formulation.

Results

Patient characteristics

A total of 191 patients were included in this analysis. The demographic and clinical characteristics are presented in Supplementary Table S1. Eighty-three percent of the participants were female, with mean (SD) age 59 (13) years, disease duration 12 (9) years, and DAS28-CRP3v 2.5 (1.0). Thirty-four percent were on biologic disease-modifying antirheumatic drugs (bDMARDs).

Differences between PGA formulations

The correlations between PGA formulations were all good, varying from $r_p = 0.65$ to $r_p = 0.80$ (all $p < 0.001$) (Supplementary Table S2).

The Bland-Altman plots showed low agreement between formulations, with 95% limits of variability ranging from [− 37.8 to + 30.4 mm (v2 vs v1)] to [− 49.7 to + 40.9 mm (v5 vs v1)] (Supplementary Fig. S1).

When comparing mean scores, the two DAS28 formulations obtained the lowest average scores (42.9 and 42.3 mm, respectively). In contrast, the formulations created by the investigators and the SDAI/CDAI resulted in the highest mean scores (48.1 and 47.2 mm, respectively), presenting a statistically significant difference ($p = 0.0003$ and $p = 0.006$, respectively) when compared with the reference (Table 1).

Ninety-nine patients (51.8%) responded to all five formulations within an interval of 20 mm. The ACR/EULAR formulation had the largest number of patients scoring ≤ 10 mm (16.2%), while the investigator's and the SDAI/CDAI formulations presented the lowest proportions (11.5 and 12.0%, respectively) (Table 1).

Differences in remission rates according to PGA formulations

When the proper formulations were used in their respective indices, the remission rates were similar in three disease activity indices: 13.1, 13.6, and 14.1%, respectively, for ACR/EULAR Boolean criteria (using v1), CDAI (using v2), and SDAI (using v2). The percentage of patients classified in remission with the DAS28-CRP (using v4) was slightly higher (18.3%) (Fig. 1). Chi-square test revealed statistically significant differences across all these proportions (Table 2).

When assessing the use of the different formulations in different indices, we observed that the ACR/EULAR formulation was associated with the highest rate of remission in all the four indices. Conversely, the SDAI/CDAI and the investigator's formulations were associated with the lowest remission rates. The maximum differences in rates of remission with the same index depending on the PGA formulation used (highest minus lowest) were as follows: 4.7% (ACR/EULAR Boolean-based), 4.7% (SDAI), 6.3% (CDAI), and 5.2% (DAS28-CRP) (Fig. 1). Considering the patients that reached at least LDA, the maximum differences between formulations ranged from 2.6 to 4.8% according to the index used (Table 3).

Discussion

This study tested how the PGA scored by individual patients with RA varies according to five different formulations of this question. We assessed the impact of these formulations upon the rates of remission and LDA defined by different disease indices. These issues have a direct impact upon treatment decisions, according to current recommendations. Although the Pearson's correlations among these formulations were good, the comparison of PGA mean values showed statistically significant differences. The 95% limits of variability revealed by the Bland-Altman plots would probably be considered as relevant by most practicing clinicians. Only approximately half of patients (51.8%) scored the five PGAs within a 20-mm interval. More importantly, differences in remission rates using different formulations of PGA for the same index were significant: for instance,

Table 1 Comparison of different PGA formulations with ACR/EULAR version as reference ($n = 191$)

Characteristics of the formulations				Comparison of mean PGA scores		n (%) of patients scoring PGA ≤ 10 mm
Source	Phrasing	Reference period	Anchors[a]	Mean (SD)	p value[c]	
v1. ACR/EULAR	"Considering all the ways *your arthritis* has affected you, how do you feel your arthritis is today?"	Today	"Very well" and "Very poor"	43.5 (28.0)	reference	31 (16.2)
v2. SDAI/CDAI	"Considering all the ways *your arthritis* affects you, rate how well you are doing on the following scale"	Unspecified time period	"Very well" and "Very poor"	47.2 (26.0)	0.003	23 (12.0)
v3. DAS original (GH)	"How *well* do you consider your *health status* during the past week?"	Last week	"The best" and "The worst"	42.9 (25.3)	0.697	27 (14.1)
v4. DAS current (DA)	"How *active* was *your arthritis* during the past week?"	Last week	"Not active at all" and "Extremely active"	42.3 (25.5)	0.400	28 (14.7)
v5. PGA formulated by the investigators	"*Your disease* has ups and downs. When it is very active ("alight," "scalded/hot"), there is more pain, morning stiffness, joint swelling and tiredness. Taking this into account, how would you rate the state of your disease over the last week?"[b]	Last week	"Not active at all" and "Extremely active"	48.1 (26.8)	0.006	22 (11.5)

ACR/EULAR, American College of Rheumatology/European League Against Rheumatism; *SDAI/CDAI*, Clinical Disease Activity Index/Simplified Disease Activity Index; *DAS*, disease activity score; *GH*, general health; *DA*, disease activity; *PGA*, patient global assessment

[a] All formulations were assessed with horizontal, unmarked visual analogue scales (0–100 mm)

[b] In Portuguese: "A sua doença tem altos e baixos. Quando está muito ativa ("acesa", "assanhada") há mais dor, prisão pela manhã, inchaço e cansaço. Tendo isto em conta, como classificaria o estado da sua doença na última semana?"

[c] Paired samples t test using, as pre-defined, the ACR/EULAR formulation as reference

ACR/EULAR Boolean-based remission varied between 8.4 and 13.1% only by switching between the five versions of PGA; this difference was highest using CDAI, with remission rates varying 13.6 and 19.9%.

Even though PGA has been widely employed in RA research [10], only few studies [11, 15–17] have examined the effect of using different formulations in the assessment of disease activity status. The main conclusions have been,

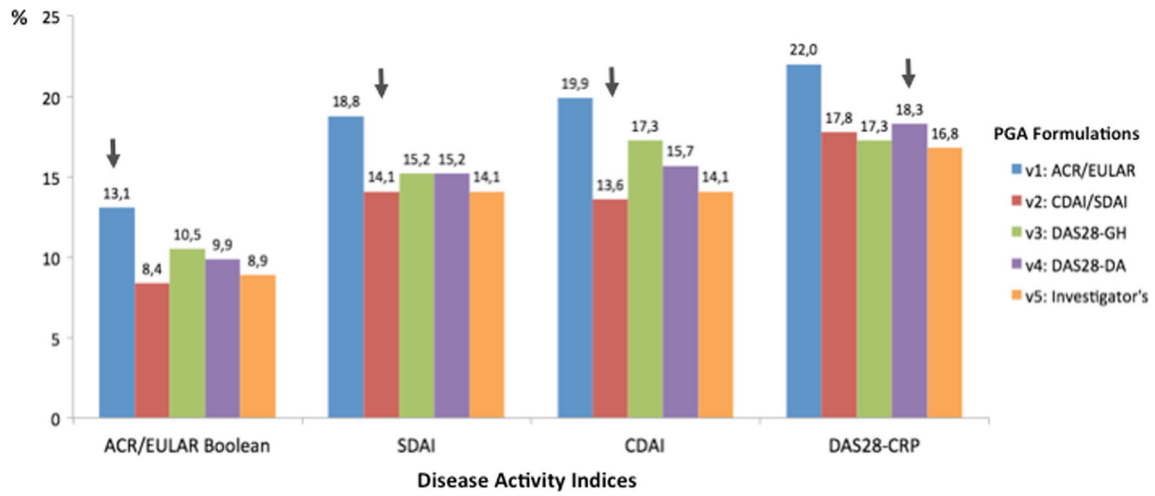


Fig. 1 Remission rates according to four disease activity indices using five different formulations of patient global assessment ($n = 191$). The arrows represent the remission rate measured by a disease activity index with its respective PGA formulation

Table 2 Comparison of the proportion of patients in remission between disease activity indices using their respective patient global assessment formulations ($n = 191$)

		ACR/EULAR Boolean-based (using v1)			Chi-square test	*p* value
		Non-Rem.	Remission	Total		
SDAI (using v2)	Non-Rem.	156	*8*	164	68.757	< 0.001
	Remission	*10*	17	27		
	Total	166	25	191		
CDAI (using v2)	Non-Rem.	156	*9*	165	62.104	< 0.001
	Remission	*10*	16	26		
	Total	166	25	191		
DAS28-CRP[a] (using v4)	Non-Rem.	146	*10*	156	33.381	< 0.001
	Remission	*20*	15	35		
	Total	166	25	191		

Figures in italic represent the discordant classification between disease activity indices

ACR, American College of Rheumatology; *CDAI*, Clinical Disease Activity Index; *DA*, disease activity; *DAS28-CRP*, disease activity score 28-joint count using C-reactive protein; *EULAR*, European League Against Rheumatism; *GH*, global health; *PGA*, patient global assessment; *SDAI*, Simplified Disease Activity Index

[a] Fleishman's et al. [6] cut-off: remission < 1.9

largely, similar in three of these studies [15–17]: although the formulations "are individually not equivalent, they may be used interchangeably for calculating composite indices" [17]. French et al. [11] suggested caution on this interchangeable use of formulations and advocated standardization of PGA. The above studies tested two [16, 17], three [15], or five [11] PGA formulations that resulted in maximum discrepancies in the remission rates of 0.5% [17], 0.9% [15], 1.3% [16], and 4.0% [11] using DAS28; 1.0% using CDAI [17]; and 0.4% using Routine Assessment of Patient Index Data 3 (RAPID3) [17]. Our study presented higher percentages of variation between formulations: 5.2% for DAS28 and 6.3% for CDAI. The main characteristics and results of the previous and present study are summarized in Supplementary Table S3.

The above-mentioned discrepancy between individual study results may be related to different factors, with

Table 3 Proportion of patients in remission and low disease activity states according to the patient global assessment formulations across different clinical disease activity indices ($n = 191$). Values represent *n* (%)

Disease activity indices	Disease activity status	PGA formulations				
		v1 ACR/EULAR	v2 SDAI/CDAI	v3 DAS28-GH	v4 DAS28-DA	v5 Investigator's
ACR/EULAR Boolean-based	Remission[a]	**25 (13.1)**	*16 (8.4)*	20 (10.5)	19 (9.9)	17 (8.9)
SDAI	Remission	**36 (18.8)**	*27 (14.1)*	29 (15.2)	29 (15.2)	*27 (14.1)*
	LDA	102 (53.4)	107 (56.0)	109 (57.1)	112 (58.6)	106 (55.5)
	Rem. + LDA	138 (72.2)	134 (70.1)	138 (72.3)	**141 (73.8)**	*133 (69.6)*
CDAI	Remission	**38 (19.9)**	*26 (13.6)*	33 (17.3)	30 (15.7)	27 (14.1)
	LDA	100 (52.4)	108 (56.5)	109 (57.1)	113 (59.2)	106 (55.5)
	Rem. + LDA	138 (72.3)	134 (70.1)	**142 (74.4)**	143 (74.9)	*133 (69.6)*
DAS28-CRP[b]	Remission	**42 (22.0)**	34 (17.8)	33 (17.3)	35 (18.3)	*32 (16.8)*
	LDA	91 (47.6)	102 (53.4)	103 (53.9)	101 (52.9)	99 (51.8)
	Rem. + LDA	133 (69.6)	**136 (71.2)**	**136 (71.2)**	**136 (71.2)**	*131 (68.6)*

Figures in bold represent the higher percentages (per line) and figures in italic represent the lowest percentages

ACR, American College of Rheumatology; *CDAI*, Clinical Disease Activity Index; *DA*, disease activity; *DAS28-CRP*, disease activity score 28-joint count using C-reactive protein; *EULAR*, European League Against Rheumatism; *GH*, global health; *LDA*, low disease activity; *PGA*, patient global assessment; *SDAI*, Simplified Disease Activity Index

[a] Low disease activity is not applicable to this definition

[b] Fleishman's et al. [6] cut-offs: remission < 1.9 and LDA ≤ 3.1

emphasis on the phrasing of the formulations. In our study, asking "(...) how do you feel your arthritis is today?" (as in ACR/EULAR) led to the highest percentage of remission. However, using a very similar formulation (as in SDAI/CDAI), but without a reference period, the opposite effect was observed. In a qualitative study from our group [18], many patients preferred being asked "today" instead of "last week" because it is easier to recall the symptoms and scoring them. It was rather surprising that the PGA formulation created by the investigators, using a more detailed and culturally adapted explanation was the one with the highest mean value and with fewer patients scoring ≤ 10 mm. A possible explanation was the inclusion of "fatigue," which patients might not otherwise consider a manifestation of RA [8]. Secondly, when using the DAS28, the effect of different PGA formulations is negligible, mostly because of the limited weight that is given to this component [16]. Finally, the levels of disease activity of the samples (influenced by the study design, among other factors) may have influenced the discrepancies, as higher levels of disease activity may be expected to be associated with larger differences between PGA formulations [16]. Our results, however, contradict this assumption given that our sample presented near half levels of disease activity but much higher discrepancies compared with previous studies (Supplementary Table S3). This suggests that culture and educational levels may play an important role in these assessments, and these influences should not be ignored [19].

One possible limitation of this study is the use of VAS instead of NRS in the SDAI/CDAI formulation. Use of VAS (rather than NRS) helped to standardize measures, and evidence from previous studies [19, 20] suggest that this would not change our conclusions. Another limitation was the presentation of formulations in the same sequence to all patients, although they were interspersed with other scales.

One important strength of our study was the use of four disease activity indices and four commonly used PGA formulations. This was also the first study to access the influence of the proper PGA formulations in the respective indices. This study used the updated cut-offs for the DAS28-CRP [6], which allowed a better comparison between the indices. Finnaly, recruiting patients from clinical practice rather than using data from a clinical trial was another advantage, as PGA instructions and interpretation by patients may be different in both contexts.

Although the added value of including PGA in the definition of disease activity remission is being debated [21, 22], it seem unequivocal, in face of our results, that each formulation of PGA should be limited to the respective disease activity index or perhaps ideally that the PGA formulation should be standardized into a unique format.

Acknowledgments We thank Sylvie Baptista and João Pedro Sousa for their help in data collection as well as Jorge Silva, Maria João Salvador, Sara Serra, Margarida Coutinho, João Rovisco, Luís Inês, Mariana Santiago, Joana Ferreira, Marília Rodrigues, Carlos Costa, Pedro Carvalho, Alexandra Daniel, Diogo Jesus, and Mary Lucy Marques (Coimbra). We also wish to thank Laure Gossec (Paris) for critically revising the manuscript for its intellectual content. We would also like to thank Tracy French, Sarah Hewlett, John Kirwan, and Tessa Sanderson for providing us supplementary information regarding their study.

Compliance with ethical standards

Ethical approval was granted by the Ethics Committee of the Faculty of Medicine, University of Coimbra (CE-037/2015). All patients signed consent according to the Declaration of Helsinki.

Disclosures None.

References

1. Smolen JS, Breedveld FC, Burmester GR, Bykerk V, Dougados M, Emery P, Kvien TK, Navarro-Compán MV, Oliver S, Schoels M, Scholte-Voshaar M, Stamm T, Stoffer M, Takeuchi T, Aletaha D, Andreu JL, Aringer M, Bergman M, Betteridge N, Bijlsma H, Burkhardt H, Cardiel M, Combe B, Durez P, Fonseca JE, Gibofsky A, Gomez-Reino JJ, Graninger W, Hannonen P, Haraoui B, Kouloumas M, Landewe R, Martin-Mola E, Nash P, Ostergaard M, Östör A, Richards P, Sokka-Isler T, Thorne C, Tzioufas AG, van Vollenhoven R, de Wit M, van der Heijde D (2015) Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. Ann Rheum Dis 75(1):3–15. https://doi.org/10.1136/annrheumdis-2015-207524
2. Felson DT, Smolen JS, Wells G, Zhang B, van Tuyl LH, Funovits J, Aletaha D, Allaart CF, Bathon J, Bombardieri S et al (2011) American College of Rheumatology/European League against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Ann Rheum Dis 70(3):404–413. https://doi.org/10.1136/ard.2011.149765
3. Smolen JS, Landewe R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M, Nam J, Ramiro S, Voshaar M, van Vollenhoven R et al (2017) EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis 76(6):960–977. https://doi.org/10.1136/annrheumdis-2016-210715
4. Singh JA, Saag KG, Bridges SL Jr, Akl EA, Bannuru RR, Sullivan MC, Vaysbrot E, McNaughton C, Osani M, Shmerling RH et al (2016) 2015 American College of Rheumatology Guideline for the treatment of rheumatoid arthritis. Arthritis Care Res (Hoboken) 68(1):1–25. https://doi.org/10.1002/acr.22783
5. van Tuyl LH, Felson DT, Wells G, Smolen J, Zhang B, Boers M, American College of Rheumatology, European League against Rheumatism Committee to Define Remission for Clinical Trials (2010) Evidence for predictive validity of remission on long-term outcome in rheumatoid arthritis: a systematic review. Arthritis Care Res (Hoboken) 62(1):108–117. https://doi.org/10.1002/acr.20021
6. Fleischmann R, van der Heijde D, Koenig AS, Pedersen R, Szumski A, Marshall L, Bananis E (2015) How much does Disease Activity Score in 28 joints ESR and CRP calculations underestimate disease activity compared with the Simplified Disease Activity Index? Ann Rheum Dis 74(6):1132–1137. https://doi.org/10.1136/annrheumdis-2013-204920

7. Martins FM, da Silva JA, Santos MJ, Vieira-Sousa E, Duarte C, Santos H, Costa JA, Pimentel-Santos FM, Cunha I, Cunha Miranda L et al (2015) DAS28, CDAI and SDAI cut-offs do not translate the same information: results from the Rheumatic Diseases Portuguese Register Reuma.pt. Rheumatology (Oxford) 54(2):286–291. https://doi.org/10.1093/rheumatology/keu313
8. Ferreira RJO, Dougados M, Kirwan J, Duarte C, de Wit M, Soubrier M, Fautrel B, Kvien TK, da Silva JAP, Gossec L et al (2017) Drivers of patient global assessment in patients with rheumatoid arthritis who are close to remission: an analysis of 1588 patients. Rheumatology (Oxford) 56(9):1573–1578. https://doi.org/10.1093/rheumatology/kex211
9. Ferreira RJO, Duarte C, Ndosi M, de Wit M, Gossec L, da Silva JAP (2017) Suppressing inflammation in rheumatoid arthritis: does patient global assessment blur the target? A practice-based call for a paradigm change. Arthritis Care Res (Hoboken) 70:369–378. https://doi.org/10.1002/acr.23284
10. Nikiphorou E, Radner H, Chatzidionysiou K, Desthieux C, Zabalan C, van Eijk-Hustings Y, Dixon WG, Hyrich KL, Askling J, Gossec L (2016) Patient global assessment in measuring disease activity in rheumatoid arthritis: a review of the literature. Arthritis Res Ther 18(1):251. https://doi.org/10.1186/s13075-016-1151-6
11. French T, Hewlett S, Kirwan J, Sanderson T (2013) Different wording of the patient global visual analogue scale (PG-VAS) affects rheumatoid arthritis patients' scoring and the overall disease activity score (DAS28): a cross-sectional study. Musculoskelet Care 11(4):229–237. https://doi.org/10.1002/msc.1046
12. Aletaha D, Nell VP, Stamm T, Uffmann M, Pflugbeil S, Machold K, Smolen JS (2005) Acute phase reactants add little to composite disease activity indices for rheumatoid arthritis: validation of a clinical activity score. Arthritis Res Ther 7(4):R796–R806. https://doi.org/10.1186/ar1740
13. van Riel PL (2014) The development of the disease activity score (DAS) and the disease activity score using 28 joint counts (DAS28). Clin Exp Rheumatol 32(5 Suppl 85):S-65–S-74
14. Bland JM, Altman DG (1986) Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1(8476):307–310
15. Dougados M, Ripert M, Hilliquin P, Fardellone P, Brocq O, Brault Y, Logeart I (2011) The influence of the definition of patient global assessment in assessment of disease activity according to the Disease Activity Score (DAS28) in rheumatoid arthritis. J Rheumatol 38(11):2326–2328. https://doi.org/10.3899/jrheum.110487
16. Koevoets R, Klarenbeek NB, Guler-Yuksel M, van Oosterhout M, van Krugten MV, Kerstens PJ, Huizinga TW, Dijkmans BA, van der Heijde DM, Allaart CF (2011) Simplified versions of the original disease activity score: validation in the BeSt trial. Ann Rheum Dis 70(8):1471–1474. https://doi.org/10.1136/ard.2010.149146
17. Khan NA, Spencer HJ, Abda EA, Alten R, Pohl C, Ancuta C, Cazzato M, Geher P, Gossec L, Henrohn D et al (2012) Patient's global assessment of disease activity and patient's assessment of general health for rheumatoid arthritis activity assessment: are they equivalent? Ann Rheum Dis 71(12):1942–1949. https://doi.org/10.1136/annrheumdis-2011-201142
18. Henriques M, Duarte C, Ndosi M, Marques A, da Silva JAP, Ferreira RJO (2017) "It can't be zero": a qualitative study of patients' perspective on patient global assessment in rheumatoid arthritis. Ann Rheum Dis 76(Suppl 2):112. https://doi.org/10.1136/annrheumdis-2017-eular.6214
19. Van Tubergen A, Debats I, Ryser L, Londono J, Burgos-Vargas R, Cardiel MH, Landewe R, Stucki G, Van Der Heijde D (2002) Use of a numerical rating scale as an answer modality in ankylosing spondylitis-specific questionnaires. Arthritis Rheum 47(3):242–248. https://doi.org/10.1002/art.10397
20. Lati C, Guthrie LC, Ward MM (2010) Comparison of the construct validity and sensitivity to change of the visual analog scale and a modified rating scale as measures of patient global assessment in rheumatoid arthritis. J Rheumatol 37(4):717–722. https://doi.org/10.3899/jrheum.090764
21. van Tuyl LHD, Boers M (2017) Rheumatoid arthritis: remission—keeping the patient experience front and centre. Nat Rev Rheumatol 13(10):573–574. https://doi.org/10.1038/nrrheum.2017.139
22. Ferreira RJO, Duarte C, Ndosi M, de Wit M, Gossec L, da Silva JAP (2018) The controversy of using PGA to define remission in RA. Nat Rev Rheumatol https://doi.org/10.1038/nrrheum.2018.35

SUPPLEMENTARY MATERIAL of

Influence of the different "patient global assessment" formulations on disease activity score by different indices in Rheumatoid Arthritis. Ferreira RJO, Eugénio G, Ndosi M, Silva C, Medeiros C, Duarte C, da Silva JAP

Contact: ferreira.rjo@gmail.com

Supplementary Table 1. Demographic and clinical characteristics of RA patients (n=191).

Variable	mean (SD)	n (%)
Age, years	59.1 (12.9)	
Number of women		158 (82.7)
Years of formal education	7.5 (4.8)	
Disease duration in years	12.4 (9.4)	
Treated with biologic agents		65 (34.2)
TJC28 (0–28)	1.5 (3.3)	
SJC28 (0–28)	1.6 (2.8)	
CRP (mg/dl)	0.8 (1.5)	
PhGA (VAS, 0-100)	13.3 (15.9)	
HAQ (0–3) [a]	1.1 (0.7)	
DAS28-CRP (3v)	2.5 (1.0)	

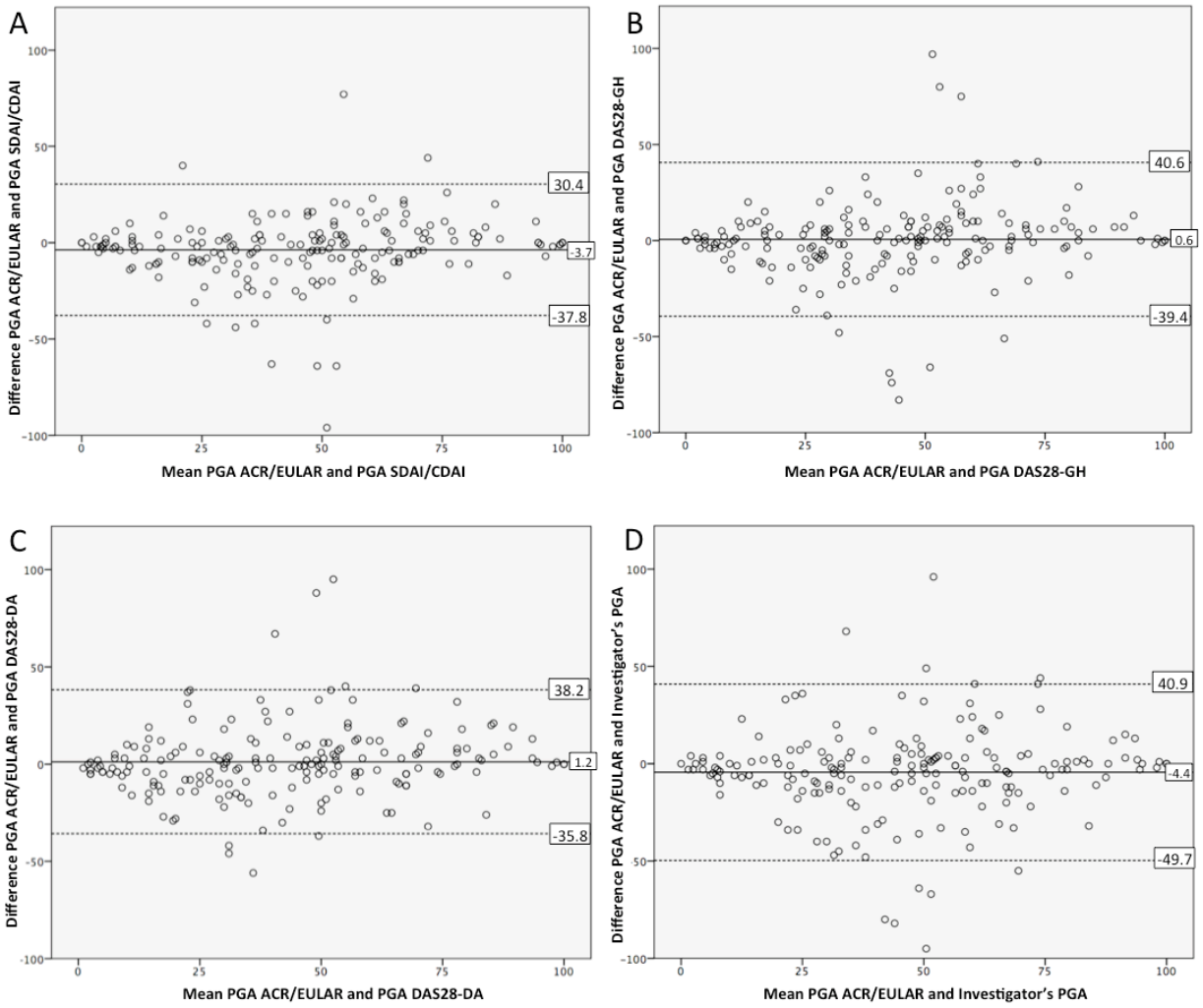
SJC28: swollen 28-joint count; TJC28: tender 28-joint count; CRP: C-reactive protein; PhGA: physician global assessment; VAS: visual analogue scale; HAQ: health assessment questionnaire; DAS28: disease activity score with 28-joint counts.
a. Missing data in 2 (1.0%) patients.

Supplementary Table S2. Pearson's correlations across the five formulations of Patient Global Assessment (n=191). All correlations were significant at p<0.001

	v2 SDAI/CDAI	v3 DAS28-GH	v4 DAS28-DA	v5 Investigator's PGA
v1 ACR/EULAR	.80	.71	.75	.65
v2 SDAI/CDAI		.67	.72	.69
v3 DAS28-GH			.76	.65
v4 DAS28-DA				.65

ACR: American College of Rheumatology; CDAI: clinical disease activity index; DA: Disease Activity; DAS28: disease activity score 28-joint count; EULAR: European League Against Rheumatism; GH: Global Health; PGA: patient global assessment; SDAI: simplified disease activity index.

Supplementary Figure S1 - Bland-Altman plots for agreement (in mm) between ACR/EULAR formulation and the other four Patient Global Assessment formulations (n=191).



ACR: American College of Rheumatology; CDAI: clinical disease activity index; DA: Disease Activity; DAS28: disease activity score 28-joint count; EULAR: European League Against Rheumatism; GH: Global Health; PGA: patient global assessment; SDAI: simplified disease activity index.

Footnote: The solid line in each plot represents the mean of the difference between the two PGA formulations. The dashed lines demarcate the upper and lower 95% limits of agreement between them, which were determined by multiplying the standard deviation (SD) of the mean difference by 1.96. In all plots, the 95% limits of agreement are considered clinically relevant., using our clinical judgements and published criteria (11, 16).

Supplementary Table S4. Main characteristics and results of studies testing the influence of different formulations of Patient Global Assessment or remission rates

Study		Patients				Disease			PGAs				Influence in remission rates		
1st author (year), Country	Design/ Analysis	n	Mean (SD) Age	% Fema-les	Educa-tional level	Disease Dura-tion	% treated biologics	Mean (SD) Disease activity	Concepts	Reference Period	Scoring Method	(Left/ Zero) Anchors	DAI used	Min.**	Max.
Koevoets (2011), The Netherlands	RCT/ Long. (1year)	467	NA	NA	NA	100% <2y	100%*	DAS Baseline#: 4.4 (0.9)	1) Global Health[1] 2) Disease Activity[2]	NA	NA	NA	a) DAS b) 6 DAS variations c) DAS28	**	a) 0.4% b) 0.2 to 1.6% c) 1.3%
Dougados (2011), France and Monaco	RCT/ Long. (12wks)	108	54 (13)	75%	NA	8 (7)	100%*	DAS28(4v) Baseline#: 5.4 (0.8)	1) Global Health[3] 2) Disease Activity[4] 3) Disease Impact (by RAID)[5]	1) Last 2-3 weeks 2) Last 48 hours 3) Last 8 days	NRS 0-10	NA	a) DAS28	a) 0.0%	a) 0.9%
Khan (2012), 30 Countries	Observ./ Cross-sectional	7023	55 (13)	80%	34% >12y	11 (10)	*NA*	DAS28: 4.3 (1.7)	1) Joint tenderness and Swelling[6] 2) Global Illness and Health[7]	1) Today 2) At this time	VAS 0-10cm	1) Not active 2) Very well	a) DAS28 b) CDAI c) RAPID3	**	a) 0.5% b) 1.0% c) 0.4%
French (2013), The UK	Observ./ Cross-sectional	50	58 (14)	78%	NA	16 (9)	92%¶	DAS28(4v): 4.3 (1.5)	1) Feeling (concerning arthritis)[8] 2) Disease Activity[9] 3) Well-Being[10] 4) Best/Worst[11] 5) All ways arthritis affect you[12]	1) Last week 2) This week 3) This week 4) Last week 5) No reference	VAS 0-100mm	1) Very well 2) Not active at all 3) Best imaginable health 4) Best have ever been 5) Very well	a) DAS28	a) 0.0%¶	a) 4.0%¶
Present Study	Observ./ Cross-sectional	191	59 (13)	83%	15% >12y	12 (9)	34%	DAS28(3v): 2.6 (1.2) DAS28(4v): 2.9 (1.3)	1) Feeling (concerning arthritis) [13] 2) How arthritis affect you[14] 3) Global Health[15] 4) Arthritis activity[16] 5) Disease (ups & downs) activity[17]	1) Today 2) No reference 3) Last week 4) Last week 5) Last week	VAS 0-100mm	1) Very well 2) Very well 3) The best 4) Not active at all 5) Not active at all	a) ACR/EULAR Boolean-based b) SDAI c) CDAI d) DAS28¶¶	a) 0.5% b) 0% c) 0.5% d) 0.5%	a) 4.7% b) 4.7% c) 6.3% d) 5.2%¶¶

ACR/EULAR: American College of Rheumatology/European League Against Rheumatism; CDAI: clinical disease activity index; DAS: disease activity score; DAS28:

disease activity score 28-joint count; NA: Non-available: PGA: patient global assessment; RAID: Rheumatoid Arthritis Impact of Disease; RAPID3: Routine Assessment of Patient Index Data 3; RCT: Randomized Controlled Trial; SDAI: simplified disease activity index.

* At the time of the analysis (i.e. at 1 year and 12 weeks, respectively); ** Applicable when 3 or more formulations were tested; ¶ Authors reported a maximum difference of 0.63 points in DAS28 in the paper but kindly provided the database to us in order to calculate these rates; ¶¶ Using Fleishman's et al.(6) cut-off: remission<1.9; ¶¶¶ If using the same cut-off of other studies (rem<2.6) the variation is the same # DAS28 values not provided for the follow-up periods (i.e. at 1 year and 12 weeks, respectively).

1 - Authors do not specify the wording in the manuscript.
2 - Authors do not specify the wording in the manuscript.
3 - "In general, how would you rate your health over the last 2–3 weeks?"
4 - "Please estimate your disease activity over the last 48 hours"
5 - The "Rheumatoid Arthritis Impact of Disease" score was used, which results from a weightned mean of 7 disease impact domains, ranging from 0 to 10.
6 - "In therms of joint tenderness (ie, joint pain associated with light touch) and joint swelling (ie, joint enlargment due to inflmation), how active would you say your rheumatic condition is TODAY?"
7 - "Considering all the ways in which illness and health conditions may affect you at this time, please make a mark below to show how you are doing"
8 - " How do you feel concerning your arthritis over the last week?"
9 - "How active has your disease been this week?"
10 - "How has your overall well-being been this week?"
11 - "If 0 is the best you have ever been and 100 is the worst you have ever been, where do you think you have been over the last week?"
12 - "Considering all the ways your arthritis affect you mark on the line bellow how well you are doing."
13 - "Considering all the ways your arthritis has affected you, how do you feel your arthritis is today?"
14 - "Considering all the ways your arthritis affects you, rate how well you are doing on the following scale"
15 - "How well do you consider your health status during the past week?"
16 - "How active was your arthritis during the past week?"
17 - "Your disease has ups and downs. When it is very active ("alight", "scalded/hot"), there is more pain, morning stiffness, joint swelling and tiredness. Taking this into account, how would you rate the state of your disease over the last week?"

Manuscript 2

"It can't be zero!" - Difficulties in completing patient global assessment in rheumatoid arthritis: a mixed methods study.

Ferreira RJO, de Wit M, Henriques M, Pinto AF, Duarte D,
Mateus E, Mendes G, da Silva JAP*, Ndosi M*

Rheumatology (Oxford). 2019 Oct 10; doi: 10.1093/rheumatology/kez467.

JOURNAL'S IMPACT FACTOR: 5.149

Number of external citations*: (In Press)

Number of self-citations*: (In Press)

CONFERENCES PRESENTATIONS/ABSTRACTS

Conference*:* EULAR Annual Congress 2017 (Madrid, Spain). Selected Oral Presentation.

Abstract*:* M Henriques, C Duarte, M Ndosi, JAP da Silva, RJO Ferreira (2017). OP0144-HPR “It can't be zero”: a qualitative study of patients' perspective on patient global assessment in rheumatoid arthritis. *Ann Rheum Dis.* 76 (Suppl 2), 112-112

- Here we presented preliminary results (n=14) of the qualitative part only

Journal's Impact Factor: 12.350

Number of external citations*: 0

Number of self-citations*: 5

Conference*:* British Society for Rheumatology Annual Conference 2019 (Birmingham, UK). Poster presentation.

Abstract*:* Ferreira RJO, Henriques M, Pinto AF, Duarte C, Mateus E, Mendes G, de Wit M, da Silva JAP, Ndosi M. (2019). 205 From zero to ten: difficulties in completing patient global assessment in rheumatoid arthritis: a mixed-methods study. Rheumatology (Oxford). 58 (Suppl 3), 126.

- Here we presented final results (n=33) of both qualitative and quantitative parts

Journal's Impact Factor: 5.245

Number of external citations*: 0

Number of self-citations*: 0

Conference*:* IV Congresso Internacional de Enfermagem Médico-Cirúrgica (Aveiro, Portugal). Oral presentation.

- Here we presented final results (n=33) of both qualitative and quantitative parts

OTHER SCIENTIFIC OUTPUTS

Editorial : This manuscript deserved an Editorial : De Cock D. & Kirsh J. (2019). The rheumatoid arthritis patient global assessment: Improve it or lose it! Rheumatology (Oxford). doi:10.1093/rheumatology/kez566

Thesis : Henriques M. (2017). Rheumatoid Arthritis - The patient perspective on Patient Global Assessment . Master in Medicine. Faculty of Medicine, University of Coimbra, Coimbra, Portugal. Available at http://hdl.handle.net/10316/82615

- This thesis presented the results obtained from data of the first 14 patients.

Visualizations*: 268 (among the 50% most viewed)

Downloads*: 267 (among the 50% most downloaded)

***** until 30th august 2019

RHEUMATOLOGY

Original article

doi:10.1093/rheumatology/kez467

'It can't be zero!' Difficulties in completing patient global assessment in rheumatoid arthritis: a mixed methods study

Ricardo J. O. Ferreira [1,2], Maarten de Wit[3,4], Marta Henriques[5], Ana F. Pinto[5], Cátia Duarte[6,7], Elsa Mateus[4,8], Gabriel Mendes[9], José A. P. da Silva [7,10,*] and Mwidimi Ndosi [11,*]

Abstract

Objectives. Patient global assessment (PGA) is purported to add the patient's perspective in the composite measures of RA. However, PGA is not standardized and it is not known whether patients' interpretation of the measure is consistent with its intended purpose. This study aimed to explore difficulties experienced by patients with RA in completing PGA, and to assess the impact of a structured explanation in improving its validity and reliability.

Methods. This was a mixed methods study, using interviews, focus groups and PGA data. During interviews, patients (convenience sample, $n = 33$) completed three often-used PGA formulations. Then a nurse provided structured explanation about what PGA is and why it is used. After further discussion, patients completed one PGA version again. Interviews were recorded, transcribed and analysed using inductive thematic analysis. We compared PGA scores pre- and post-explanation (Wilcoxon signed-ranks) and the proportion of patients achieving RA remission with PGA $\leqslant 1$ (McNemar's tests).

Results. Three themes emerged: understanding the meaning of PGA, the purpose of PGA and measurement difficulties. The difficulties caused systematic errors in PGA completion such as marking higher when feeling well, marking near the centre or away from zero. The structured explanation was helpful. Following the explanation, the median PGA score decreased from 3.0 to 2.1 cm, and the proportion of non-remission solely due to PGA >1 from 52% to 41%; none of these changes was statistically significant.

Conclusion. Many patients have difficulties in completing PGA. Standardization of PGA and a structured explanation may improve its clarity, validity and reliability.

Key words: nursing, mixed method study, patient education, outcome assessment, patient-reported outcome measures, remission, rheumatoid arthritis

CLINICAL SCIENCE

Rheumatology key messages

- Many patients with RA are unaware of the purpose of patient global assessment.
- Patients have difficulties in completing patient global assessment reliably, thus undermining the validity of the measure.
- A standardized formulation and giving a structured explanation to the patient may improve the validity of patient global assessment.

[1]Rheumatology Department, Centro Hospitalar e Universitário de Coimbra, Coimbra, [2]Health Sciences Research Unit: Nursing (UICiSA: E), Nursing School of Coimbra (ESEnfC), Coimbra, Portugal,[3]Department of Medical Humanities, Amsterdam University Medical Centre, Amsterdam, The Netherlands, [4]Patient Research Partner, EULAR standing committee of People with Arthritis/Rheumatism in Europe (PARE), Zurich, Switzerland, [5]Faculty of Medicine, University of Coimbra, Coimbra, [6]Rheumatology Department, Centro Hospitalar e Universitário de Coimbra, Coimbra, [7]Coimbra Institute for Clinical and Biomedical Research (iCBR), Faculty of Medicine –University of Coimbra, Coimbra, [8]Portuguese League Against Rheumatic Diseases (LPCDR), Lisbon, [9]Department of National Team, Portuguese Cycling Federation, Lisbon, [10]Rheumatology Department, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal and [11]Department of Nursing and Midwifery, University of the West of England, Bristol, UK

Submitted 2 July 2019; accepted 20 August 2019

*José A. P. da Silva and Mwidimi Ndosi contributed equally to this study.

Correspondence to: Ricardo J. O. Ferreira, Serviço de Reumatologia, Consulta Externa, Piso 7, Centro Hospitalar e Universitário de Coimbra, EPE. Avenida Dr. Bissaya Barreto, 3000-075 Coimbra, Portugal. E-mail: rferreira@reumahuc.org

Introduction

Patient global assessment (PGA) is a self-report measure widely used in rheumatology [1] and in other long-term conditions such as neurology [2], cardiology [3], psychiatry [4], dermatology [5] and gastroenterology [6]. PGA is meant to generally reflect a patient's own assessment of the severity of their condition, and is included in disease activity indices used to guide therapy decisions.

It is hard to identify when and how PGA was developed, but initially it was designated as 'global health', with the earliest references in PubMed dating from 1977 [7] and 1980 with the studies on the 'Arthritis Impact Measurement Scales' [8]. The use of PGA was boosted in the early 1990s by its inclusion in the widely implemented DAS [9, 10] and in the ACR core set of disease activity measures for RA clinical trials [11]. The incorporation of PGA in these composite measures was justified, mainly, by its high sensitivity to change, as documented in meta-analyses [12] or in other comparative studies [13]. PGA is also practical and easy to administer, and has good face validity and test–retest reliability. It provides additional information to the clinician (patient perspectives of disease activity) [1]. These strengths have made PGA the second most used patient-reported outcome in RA clinical trials next to the HAQ [14, 15]. In 2011, the ACR and the EULAR defined the criteria for RA remission, which attributed to PGA the same weight as that of tender and swollen joint counts (TJC28, SJC28) and inflammatory markers (CRP), all required to be $\leqslant 1$ [16]. This reflects the growing significance of the patient's perspective because the current pharmacological management of RA resides in treating to target, the target being remission [17, 18].

Incorporating PGA in composite indices did not happen without controversy. Its validity and reliability have been questioned [19–22]. There are many versions of PGA, which ask about different concepts ('Considering all the ways the *disease* affects you …', 'Considering all the ways your *arthritis* has affected you …' 'How well do you consider your *health state* …' 'How active was your *arthritis* …'), different time references (today, past week) and different anchor descriptors ('Doesn't affect–Affects a lot', 'Very well–Very poor', 'The best–The worst') [1, 23]. One of the main concerns is the interchangeable use of different PGA formulations, and this has been shown to influence the remission rate up to 6.3% among disease activity indices [23]. A recent systematic review [1] indicates that many studies still test the properties and concepts underlying PGA. Recent research has shown that PGA is predominantly related to disease impact domains (pain, fatigue, functional disability and psychological distress) rather than to disease activity itself (inflammatory markers) [24], thus questioning the validity of incorporating PGA in RA remission definitions [23–25]. This led to a proposal to remove PGA from the RA remission definition, which has also been controversial [26, 27]. Understanding what patients consider when they answer the PGA question may help shed light in this on-going debate.

The aims of this study were to explore patients' difficulties in completing PGA, and to explore the impact of a structured explanation about PGA, with the purpose of improving its validity and reliability.

Methods

Design

This was a mixed methods study with a 'qualitative dominant' component [28]. Qualitative and quantitative data were concurrently collected and analysed separately before integration in the interpretation phase [29]. Qualitative data were obtained by semi-structured individual interviews and focus groups. Quantitative data were obtained from participants' responses to three different formulations of PGA (see 'Data collection' below), used to facilitate discussions, one of which was repeated after a structured explanation (see 'Intervention' below).

Participants

Consecutive sampling was used to recruit adult patients satisfying current RA criteria [30, 31] via one rheumatology clinic centre in a large university hospital in the centre of Portugal. Patients were excluded if they were unable to read and answer the questionnaires unaided.

Intervention

The intervention consisted of a brief (<5 min) structured explanation on (i) what is expected to be captured by PGA, i.e. what the patient feels is affecting his/her well-being as a consequence of the RA, or in other words, caused/triggered by active 'inflammation', such as swelling in joints, pain, stiffness, fatigue, that is not likely caused by other medical conditions (examples were provided); (ii) how PGA is included in disease activity indices (DAS28 and Simplified Disease Activity Index); and (iii) how these composite indices are used to guide treatment decisions. The structured explanation was first pretested with three participants, leading to simplification in the wording. The first author (R.J.O.F., a registered nurse) delivered the intervention using visual aids (see supplementary Fig. S1A–H, available at *Rheumatology* online).

Data collection

Data collection was performed between November 2016 and January 2017. An interview guide (see supplementary Table S1, available at *Rheumatology* online) was developed by the research team, pilot-tested with three patients not included in the sample, and used in both individual interviews and focus groups.

First, participants completed a form with their demographic and clinical data and they were requested to complete one formulation of PGA to prompt discussion. Two additional versions of PGA were applied, one at a time. The three formulations were selected for their variances in concept and time-frame under evaluation, all using a visual analogue scale (VAS, 0–100 mm): version 1—'Considering all the ways the disease affects you, how did you feel over the last week?' [8] (anchors:

'Doesn't affect'–'Affects a lot'), version 2—'Considering all of the ways your arthritis has affected you, how do you feel your arthritis is today?' [16] ('Very well'–'Very poor') and version 3—'How would you assess your health state during the past week?' [9, 10] ('The best'–'The worst'). For each version, participants were asked to carefully read the question, mark their answer and then to reflect in silence and write down their thoughts and key words. Following the discussion of the three formulations, the intervention was given and participants were asked to discuss again. Finally, the participants were asked to re-assess version 2 of PGA, as this is the most accepted version [1, 16].

An experienced and trained qualitative researcher and interviewer (R.J.O.F.) led the discussion. All interviews took place in a quiet room in the rheumatology department. The interviews took ~35–40 min and were audio taped and anonymized (P1 to P33) at transcription, completed with field notes.

The disease activity on the day of the interview was derived from clinical records in order to assess the influence of PGA on the remission status. The ACR/EULAR Boolean-based definition of remission [16] and the following categories were used: remission: SJC28, TJC28, CRP in mg/dl, and PGA all $\leqslant 1$; PGA-near-remission: only PGA is >1; and non-remission: SJC28, TJC28, or CRP in mg/dl are >1 [24].

The study adhered to Good Clinical Practice in research and the Ethics Committee of the Centro Hospitalar e Universitário de Coimbra, Portugal, approved the study (CHUC-093-16). Participants provided written informed consent before study procedures started.

Data analysis

Inductive thematic analysis [32, 33] was used to ensure that qualitative findings were grounded in patients' data. Transcripts were made a few days after interviews and were read and reread by the first author to gain an understanding of, and familiarization with, the issues and patterns. Then, small units of meaning were identified line-by-line and given descriptive labels (codes). Next, the findings were explored to see how codes could be grouped to form categories and/or overarching themes. Data management and analysis were facilitated by ATLAS.ti v.1.0.51 software (Scientific Software Development GmbH, Berlin).

For analysis of the quantitative data we used the Wilcoxon rigned-ranks test to compare PGA scores before and after the intervention, and McNemar's test to compare the proportion of PGA-near-remission patients before and after the intervention. IBM® SPSS® Statistics, version 20.0 software (IBM Corp., Armonk, N.Y., USA) was used.

Validity and reliability/rigour

The qualitative data analysis was carried out independently by two researchers (R.J.O.F. and M.H.), who later discussed and subsequently agreed on codes and themes. The resulting categorization and data interpretation was discussed and improved with the wider research team, which included three nurses, three patient research partners, two rheumatologists and one medical student. The resulting themes were presented to 10 of the 33 participants for validation of the data interpretation made by the researchers.

Results

Patient characteristics

Forty patients were invited to the study but seven declined participation. Of the 33 participants, 7 were interviewed individually and 26 took part in eight focus groups. Participants' age range was 42–82 years, disease duration 1–48 years and 76% were women. Table 1 presents participants' characteristics.

Qualitative findings: difficulties experienced by patients in completing PGA

Three overarching themes emerged from the qualitative data analysis: understanding the meaning of PGA, measurement difficulties and understanding the purpose of PGA. The categorization is visualized in Fig. 1 and themes are presented below, supported by quotes. Additional quotes are presented in Tables 2–4.

Understanding the meaning of PGA

When discussing what participants thought about or considered when completing the PGA, pain was clearly the most-often mentioned symptom. Pain limited their daily activities, such as self-care, walking, climbing stairs, work and participation activities (Table 2).

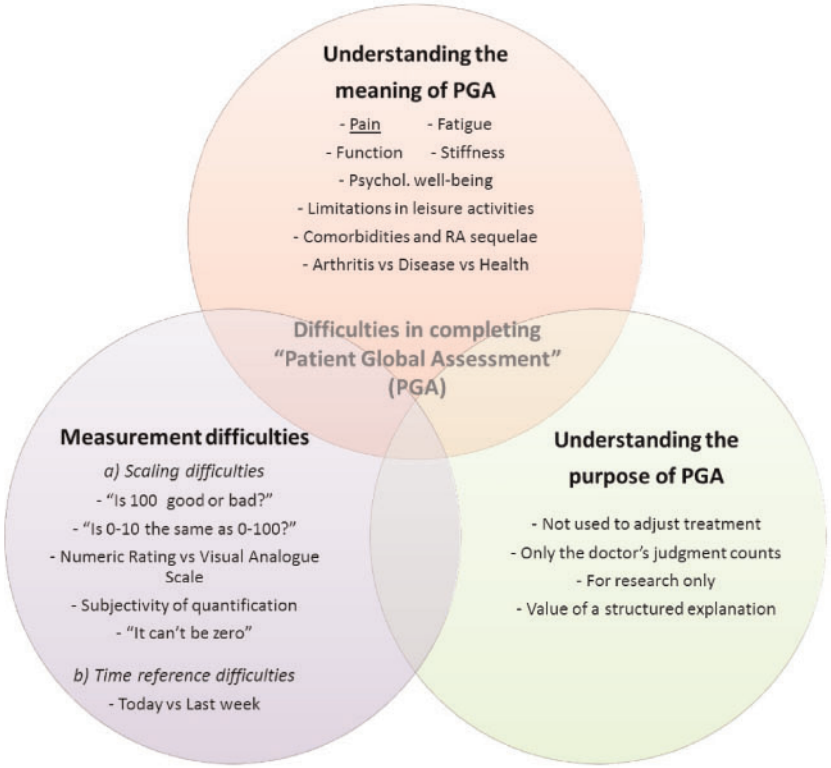
Other symptoms that participants associated with RA were fatigue, limitations in leisure activities, stiffness or psychological distress. Regarding fatigue, the participants did not know whether or not it was associated with RA, but they found it affecting many aspects of life such as work, self-care, walking, thinking or even talking. The psychological distress encompassed a spectrum of disease-related anxieties, from fears that arose with the diagnosis or with blood tests to suicide ideation (Table 2).

Table 1 Participant's characteristics ($n = 33$)

Variable	*N* (%)
Gender (female)	25 (76)
Age, years	
42–52	6 (18)
53–62	12 (36)
63–72	12 (36)
73–82	3 (9)
Education background, years	
$\leqslant 4$	15 (46)
5–9	10 (30)
10–12	6 (18)
>12	2 (6)
Disease duration, years	
1–5	8 (24)
6–10	4 (12)
>10	21 (64)
Treated with bDAMRDS, yes	12 (36)

bDMARD: biological DMARD.

Fig. 1 Overarching themes and codes of participant's difficulties in completing patient global assessment (PGA)



> 'The pain upsets me, the tiredness, the fact that I can't do my life, I thought I was going to be disabled. I think about suicide.' (P31)

Participants also considered how some comorbidities and RA sequelae affected their PGA score. One example given was how difficult it was to ascertain the origin of pain, although PGA requires only the pain/discomfort caused by RA to be considered:

> '(. . .) we always have to think about the joints, the joints and not the spine, for example, an herniated disc (. . .). Because when we read this we need to see ''it's only arthritis''. So, I have to try to distinguish and sometimes we don't even think about it.' (P5)

The meaning of PGA was also complicated by the use of different PGA formulations, namely by the terminology arthritis *vs* disease *vs* health. Although for some patients the three words are similar—'To me, there's no difference' (P10)—most participants considered them to address different concepts. It was also mentioned that this might be particularly difficult for people affected by depression.

> 'Health involves my head too. It's not only arthritis for sure.' (P7)

> 'The disease is everything in general, right? Not just the arthritis itself. The arthritis is the arthritis! The health one is everything again, right?' (P8)

Measurement difficulties

Several measurement issues emerged from the interviews and these are presented in two sub-themes: scaling difficulties and time reference difficulties (Table 3).

Scaling difficulties. At least three participants completed the VAS without paying attention to the anchor descriptors, assuming that 10 cm (or 100 mm) is good (similar to 'feeling 100%'). Others felt confused by the anchors after completing several questionnaires, some with similar questions but opposite anchors. The question as to whether 100 is good or bad was often raised. Some participants expressed difficulties with the scaling conversion, questioning whether 0–10 was the same as 0–100. The presentation of PGA through numeric rating scale *vs* VAS also causes difficulties of interpretation for some patients (Table 3).

> 'I always put 100 which is good (. . .). There are other [scales] where zero is good and 100 isn't, it depends on how they put it. In this case right here I think 100 is the good one.' (P2)

The subjective nature of the concept being assessed (PGA) was also pointed out as a difficulty because the quantification of a feeling or sensation or impact of disease is very different from individual to individual:

> 'It also depends from person to person, there are some more mushy (. . .) It has happened to me: [the

Table 2 Quotes supporting the theme 'Understanding the meaning of PGA' and its different codes

Codes	Quotes (participant details)
Pain	'I think about pain because that's what worries me the most' (P9, F, 66y, PGA = 4.5, non-remission) 'Yes, I thought about the pain in my hand (. . .) Everyday it hurts in a different site' (P20, F, 71y, PGA = 1.9, near-remission) '(. . .) I can't work with so much pain (. . .) I want to do my daily activities and I can't' (P15, F, 60y, PGA = 7.1, non-remission)
Fatigue	'I feel very tired, I do my job but in the end I feel exhausted (. . .) perhaps it is due to the disease (. . .) but I'm not sure, is it?' (P1, F, 72y, PGA = 2.0, non-remission) 'It's a fatigue even to talk' (P12, F, 47y, PGA = 7.9, near-remission)
Function	'Two weeks ago I could brush my hair but, in the meantime I stopped being able and had to cut it' (P31, F, 61y, PGA = 9.9, non-remission) 'Lately I have to go down stairs with both feet on the same step' (P2, F, 55y, PGA = 5.3, non-remission) 'I couldn't tight the buttons in my clothes or even dress myself' (P26, M, 62y, PGA = invalid, near-remission)
Stiffness	'In the morning I feel my joints very stuck for 2 hours and it's a lot harder for me to do my normal life as I used to' (P2, F, 55y, PGA = 5.3, non-remission)
Psychological well-being	'I worry more about the discomfort, feeling bad, than with the pain itself. (. . .) maybe it is more a psychological issue. I can't feel good about myself anymore (. . .) Your self-esteem is also affected and accounts to it' (P5, F, 59y, PGA = 3.8, near-remission)
Leisure limitations	'I pondered if I would be able to talk a walk by the sea, it wasn't the pain, it was the discomfort, how would I (. . .)? (P5, F, 59y, PGA = 3.8, near-remission)
Comorbidities and RA sequelae	'It's the lack of strength [in my hands], I still have sensitivity' (P14, M, 66y, PGA = 7.5, non-remission) 'I thought, I do not know if it's because the medication but I get tremors. And at night I get up a lot because of the pain and because I can't find a comfortable position' (P24, F, 75y, PGA = invalid, non-remission) 'I have pain in my arms but that's due to tendonitis, I should have had physiotherapy' (P32, F, 56y, PGA = 0.6, remission) 'I have osteoarthritis all over the body' (P21, F, 73y, PGA = 5.9, near-remission)
Arthritis *vs* disease *vs* health	'Disease is a general thing. Here for example I noticed that it's only the arthritis that matters. Because if you have a colic, it's a disease, right?' (P5, F, 59y, PGA = 3.8, near-remission) '(. . .) this only refers to arthritis I don't have to include [the pain caused by an herniated disc]' (P27, F, 52y, PGA = 4.5, near-remission) 'It's not that easy. It's almost all the same' (P27, F, 52y, PGA = 4.5, near-remission) 'Sometimes we ask if the doctor wants us to evaluate our disease in general and he says no, that he only wants us to think about the arthritis' (P5, F, 59y, PGA = 3.8, near-remission)

Remission is defined by SJC28, TJC28, CRP and PGA all $\leqslant 1$; near-remission, only PGA is >1; non-remission, SJC28, TJC28 or CRP are >1. Version 2 of PGA was considered for this definition. PGA: patient global assessment; F: female; M: male; y: years; SJC28: swollen 28-joint count; TJC28: tender 28-joint count; P: participant.

> doctor says] ''oh, you don't have complaints? You have everything inflamed. You're very tough.'' ' (P3)

Scoring in the extremes, especially the minimum, was very rare and some participants clearly stated: 'It can't be zero'. Different reasons given were: (i) the fear that scoring the PGA near to zero could lead to the withdrawal of medications, especially the expensive biological DMARDs; (ii) the presence of comorbidities and RA sequelae (e.g. thumb OA) that will never allow the patient to be in a perfect health status; (iii) patients want to take into account the fluctuating nature of RA disease activity. Therefore, some participants felt the need to refrain from considering a score of zero or near to it, even when they had no active disease.

> 'I can never answer 0, because I always have something that affects me. Someday I feel nothing, it goes well, but on other days the pain comes back from nowhere.' (P29)

Time reference difficulties. Different PGA formulations refer to different time reference: over the last week (versions 1 and 3) and today (version 2). This raised assessment problems and for most participants it was easier answering about today than trying to 'average' the last week, which can be subject to a recall bias.

> '[Today] is different from the week (. . .) it's definitely easier. When they ask a week, we have to go back in time and the pain isn't the same anymore (. . .) And today, it is easy to remember.' (P5)

Naturally, patients express that assessing only one day ('today') instead of a week is less representative of the disease burden, and more often lower, which depends on whether the symptoms fluctuated or not.

It also seems that when asked about 'today' patients are more likely to recall all their disease history as reference, or in other words, they seem to interpret 'today' as 'nowadays' in opposition to the time of the disease onset.

Table 3 Quotes supporting the theme 'Measurement difficulties' and its different codes

Sub-theme	Codes	Quotes (participant details)
Scaling difficulties	'Is 100 good or bad?'	'So you answered your health is very bad, wasn't it?' (Interviewer) 'No, here I answered [patient reads again PGA3] 100% is (. . .) oooh, it's worse! I'm sorry, I don't read (. . .) Can I change it? (. . .) I don't know, I thought that way because the other question was about the pain [PGA1—disease], the pain was 100%. Here [PGA3] I thought the same way, your health is either 0 or 100%. That's my interpretation (. . .) that I was completely fine with 100%' (P3, F, 49y, PGA = 2.2, non-remission)
		'So here the 100 is very well isn't it? (. . .) [looks at the question again] Here it's (. . .) it's the confusion that this is' (P6, F, 70y, PGA = 2.0, near-remission)
		'In this scale the 0 is good, the 100 is bad, it depends on the way you put it. In this case right here I always think that 100 is the good one' (P2, F, 55y, PGA = 5.3, non-remission)
	'Is it 0–10 the same of 0–100?'	'Sometimes I don't understand the question. I don't understand if it's 0 to 10 or 0 to 100. I get confused with this, I don't know' (P6, F, 70y, PGA = 2.0, near-remission)
		'(. . .) usually I've to answer from 1 to 10' (P30, F, 61y, PGA = 0.7, remission)
	NRS *vs* VAS	'It's here? It's to write a mark? (. . .) Usually it's with the numbers, 0 to 100'. (P5, F, 59y, PGA = 3.8, near-remission)
		'Usually it has the numbers (. . .) It's not like a straight line like this one' (P2, F, 55y, PGA = 5.3, non-remission)
	Subjectivity of quantification	'Sometimes [the answers are not honest] because we [the patients] don't understand, because we don't know how to evaluate the pain itself' (P5, F, 59y, PGA = 3.8, near-remission)
		'(. . .) sometimes a person can be very well in the blood tests and have pain, I think (. . .) because it has happened to me, and the opposite, everything swollen and [the doctors] ''So it's not hurting?'' they push and it doesn't hurt' (P2, F, 55y, PGA = 5.3, non-remission)
	'It can't be zero!'	'Usually I answer 2 or 3 (. . .) sometimes I don't feel any pain at all, and I always answer 2 or 1, just by thinking of the day after. (. . .) We're always waiting for the worst!' (P2, F, 55y, PGA = 5.3, non-remission)
		'No, it can't be 0. The psychic also counts, it's very important (. . .)' (P5, F, 59y, PGA = 3.8, near-remission)
		'(. . .) [I can ever answer 1] (. . .) look at my hand for example, this is all arthritis. If I have my self-esteem' (P6, F, 70y, PGA = 2.0, near-remission)
Time reference difficulties	Today *vs* last week	'Uhhh the most adequate (. . .) may be this one ['today'] Because in the last week the pain has already gone, and today I'm still feeling it (P28, M, 55y, PGA = 2.2, near-remission)
		'When we are told a week, we have to backtrack far behind and no longer intensify or decrease the pain. Because you are no longer feeling. And today when we get up in the morning, the space that takes us between morning and now (. . .) is so recent' (P5, F, 59y, PGA = 3.8, near-remission)
		'I prefer this one ''how I feel today'' because it's simpler than remembering the other days (. . .) if I feel good today I try to forget what happened before' (P30, F, 61y, PGA = 0.7, remission)
		'Today, compared to what I felt before (. . .) Today I am much better (. . .) but maybe I did not think about the week that I felt less pain, I thought about a long time ago' (P3, F, 49y, PGA = 2.2, non-remission)
		'I think (. . .) it's more or less the same thing today or within the last week' (P8, F, 58y, PGA = 1.3, near-remission)

Remission is defined by SJC28, TJC28, CRP and PGA all $\leqslant 1$; near-remission, only PGA is >1; non-remission, SJC28, TJC28 or CRP are >1. Version 2 of PGA was considered for this definition. NRS: numeric rating scale; PGA: patient global assessment; VAS: visual analogue scale; F: female; M: male; y: years; SJC28: swollen 28-joint count; TJC28: tender 28-joint count; P: participant.

> ' ''last week'' is what happened last week and the other one [PGA2 – 'today'] is since I was diagnosed with RA.' (P12)

Understanding the purpose of PGA

None of the participants had knowledge about how the PGA score is integrated in composite disease activity indices such as DAS28 and how this would affect the selection or adjustment of their treatment. Only a few participants mentioned that the PGA would serve to adjust their treatment, but most of them had the feeling the PGA is 'not used to adjust the treatment', but rather used to assess patient psychological well-being, disease evolution or to identify any complication that might preclude biological DMARD administration (Table 4).

> 'I thought it [the PGA] was only meant to check on how we were feeling (. . .) for psychological evaluation (. . .) That it had no influence (. . .)'(P10)

Table 4 Selection of quotes supporting the theme 'Understanding the purpose of PGA' and their different codes

Codes	Quotes (participant details)
Not used to adjust the treatment	'I think it matters, for a better evaluation of the patient. And that it can influence (. . .) the treatment' (P28, M, 55y, PGA = 2.2, near-remission)
	'Honestly? I think the doctor sometimes asks that only as a routine – he doesn't really value it (. . .) Because at the same time, he's asking me that, he's already writing on the computer. He doesn't look me in the face. We only say yes or no' (P5, F, 59y, PGA = 3.8, near-remission)
	'I think it is important [the PGA]. The questions made are important because (. . .) sometimes if we have some disturbing situation, this medication [biological therapy] can't even be administered' (P8, F, 58y, PGA = 1.3, near-remission)
Only the doctor's judgment counts	'The doctor considers the blood analysis, evaluates the swelling, the spine movements and so on. And the question [PGA] is one more thing to have in account' (P19, M, 70y, PGA = invalid, non-remission)
	'(. . .) We make the blood tests, the doctor does the [joint] counting, (. . .) if I give one answer that doesn't accord at all with that, obviously they might ignore me, or at least they become aware that we don't know what we have (. . .)' (P3, F, 49y, PGA = 2.2, non-remission)
	'Our correct and honest answer will help a lot in the analysis and the counting of the articulations' (P5, F, 59y, PGA = 3.8, near-remission)
	'If she [the doctor] thinks I'm worse she will increase the medication' (P15, F, 60y, PGA = 7.1, non-remission)
For research only	'[PGA fits out To study, I don't know, I don't understand (. . .) why you [health professionals] ask that' (P2, F, 55y, PGA = 5.3, non-remission)
	'For me it's to evaluate. I think that is for them, for the doctors, to know if these recent treatments, in fact, worth or not' (P3, F, 49y, PGA = 2.2, non-remission)
Value of a structured explanation	'I didn't knew what was the purpose [of the PGA] (. . .) I knew the joints evaluation was to be possible for the doctor to see the evolution but I didn't knew the intention was to add that' (P3, F, 49y, PGA = 2.2, non-remission)
	'Although I always answered carefully because I knew it was important, I wasn't aware of its impact on the treatment' (P33, F, 42y, PGA = 9.8, near-remission)
	'I was somewhat aware because my husband likes to search and read. I have books to read (. . .) to get to know' (P1, F, 72y, PGA = 2.0, non-remission)
	'Now that you're explaining it to me, I will take that into account in the next evaluation' (P2, F, 55y, PGA = 5.3, non-remission)

Remission is defined by SJC28, TJC28, CRP and PGA all $\leqslant 1$; near-remission, only PGA is >1; non-remission, SJC28, TJC28 or CRP are >1. Version 2 of PGA was considered for this definition. PGA: patient global assessment; F: female; M: male; y: years; SJC28: swollen 28-joint count; TJC28: tender 28-joint count; P: participant.

Some participants also expressed the view that 'only the doctor's judgment counts', meaning that they were asked to complete PGA only to confirm the rheumatologist's opinion, which is based on objective measures of disease. They felt that the PGA would not be considered if it contradicted the doctor's perceptions; that is, the doctor had already made his decision.

> 'It will [influence the treatment] if the answer is somehow according to the blood tests we make. If it doesn't agree, maybe it's not important.' (P3)

> 'Honestly? I think the doctor sometimes asks that only as a routine – he doesn't really value it (. . .)'(P5)

Other participants considered that PGA is used 'for research only', namely to evaluate the efficacy of new treatments.

After the intervention, individually patients confirmed the value of a structured explanation, suggesting that this information was new to them and that it would influence their subsequent assessments.

> 'Sometimes I just give a random number (. . .) now maybe I will think more carefully and try to be as accurate as possible.' (P4)

Quantitative results

Pre- vs post-intervention differences on PGA score and on remission classification

After the structured explanation, 15 (51.7%) participants decreased their PGA scores, while 9 (31.0%) increased them, and 5 (17.3%) gave exactly the same score given before the intervention (Table 5). The median (interquartile range) PGA scores before and after the intervention were 3.0 (1.4–6.9) cm and 2.1 (1.0–5.9) cm, respectively. These differences were not statistically significant ($Z = 104$, $P = 0.188$).

Before the intervention, only five patients (17.3%) satisfied the ACR/EULAR Boolean-based remission criteria but after the intervention eight patients (27.6%) attained this state. The proportion of patients failing Boolean-based remission solely because of a PGA >1 was 52% pre-intervention and 41% post-intervention (Table 5), a difference that was not statistically significant ($P = 0.375$).

Discussion

This study has shown that an instrument widely used in rheumatology, PGA, has considerable assessment and

Table 5 Disease activity and patient global assessment scores before and after the intervention

	Disease activity				PGA scores (0–10 cm)		
Patient number	TJC28	SJC28	CRP (mg/dl)	ACR/EULAR Boolean remission[a] Pre- and (→) post-intervention	PGA pre-intervention[b]	PGA post-intervention[b]	Post- minus pre-intervention
P1	3	2	0.50	Non-remission	2.0	2.0	0
P2	3	2	1.02	Non-remission	5.3	5.7	+0.4
P3	3	0	0.02	Non-remission	2.2	2.2	0
P4	0	0	0.02	Near-remission → remission	3.0	0.9	−2.1
P5	0	1	0.21	Near-remission	3.8	2.0	−1.8
P6	0	0	0.30	Near-remission	2.0	1.7	-0.3
P7	0	1	0.02	Near-remission	1.1	2.4	+1.3
P8	0	0	0.02	Near-remission	1.3	2.1	+0.8
P9	0	0	1.31	Non-remission	4.5	3.8	−0.7
P10	0	0	0.02	Remission	0.3	0.4	+0.1
P11	1	1	0.04	Near-remission	4.9	3.7	−1.2
P12	0	0	0.13	Near-remission	7.9	6.0	−1.9
P13	0	0	0.10	Remission	0.2	0.2	0
P14	2	2	0.27	Non-remission	7.5	8.2	+0.7
P15	2	0	0.27	Non-remission	7.1	8.0	+0.9
P16	4	0	0.93	Non-remission	6.6	7.5	+0.9
P17	1	1	0.57	Remission	0.2	0.3	+0.1
P18	0	0	0.23	Near-remission	8.8	8.8	0
P19	2	2	1.8	–	invalid	invalid	–
P20	0	0	0.36	Near-remission	1.9	1.5	−0.4
P21	0	0	0.51	Near-remission	5.9	5.8	−0.1
P22	0	1	0.59	Near-remission → remission	1.5	1.0	−0.5
P23	0	0	0.23	–	invalid	invalid	–
P24	0	0	1.20	–	invalid	invalid	–
P25	2	1	0.63	Non-remission	7.3	7.0	−0.3
P26	0	0	0.26	–	invalid	invalid	–
P27[c]	0	0	0.13	Near-remission	4.5	3.2	−1.3
P28[c]	0	0	0.42	Near-remission	2.2	1.9	−0.3
P29[c]	0	0	0.47	Near-Remission → remission	1.6	0.8	−0.8
P30[c]	0	0	0.20	Remission → near-remission	0.7	1.7	1.0
P31[c]	9	8	1.20	Non-remission	9.9	9.3	−0.6
P32[c]	0	1	0.26	Remission	0.6	0.6	0
P33[c]	0	0	0.07	Near-remission → remission	9.8	0.2	−9.6
Total	73%, ⩽1	85%, ⩽1	85%, ⩽1	Near-remission = 52% (pre-) and 41% (post-intervention)	17%, ⩽1	28%, ⩽1	57% pre- > post-intervention

[a]Remission is defined by SJC28, TJC28, CRP and PGA all ⩽1; near-remission, only PGA is >1; non-remission, SJC28, TJC28 or CRP are >1. Version 2 of PGA was considered for this definition. [b]Version 2: 'Considering all of the ways your arthritis has affected you, how do you feel your arthritis is today?' [c]These participates were interviewed individually. PGA: patient global assessment; SJC28: swollen 28-joint count; TJC28: tender 28-joint count.

interpretation issues. This mixed-methods approach allows a better understanding of several difficulties experienced by patients with RA when completing this measure. The overall results suggest that we cannot be sure whether PGA provides a valid representation of what it is intended to measure and that there is a need for a standardized version. This study has increased our understanding of the impact of the interchangeable (unstandardized) use of different formulations of PGA on the scores given by patients. These are likely to have consequences on disease activity assessment and may affect subsequent treatment decisions. This was also the first study to explore the effect of a relatively simple and brief intervention (a structured explanation about PGA, given by a nurse) on the scores of PGA and the proportion of patients attaining remission.

The qualitative analysis resulted in three themes explaining the difficulties in completing the PGA. First,

participants had difficulties in understanding the meaning of PGA. The vast majority of the participants identified pain as the main factor that was associated with disease activity, followed by function, fatigue, psychological well-being and other symptoms. They found it hard to exclude from consideration both comorbidities and sequelae of RA. These results are in accordance with previous quantitative and qualitative research [34–39]. The influence of contextual factors (not directly related to RA inflammation) upon PGA, such as psychological distress, coping and comorbidities, is also well documented [1, 24, 38–40].

Second, there were difficulties related to the measurement of PGA. Different measurement scales such as the use of entire numbers (numeric rating scale) or a continuous line to select one specific point (VAS) have been shown to require different levels of conceptualization from the patient, with the first being easier to understand and mark. Some patients frequently assume that the anchors are always the same and many spontaneously adopt the right side or the higher number, especially 100 ('100%'), as meaning a better status. This issue has also been identified in other instruments [41] and diseases [42]. This may be explained to some extent, by the principles of the Gutenberg Diagram, which describes the visual hierarchy and mind motion variations according to cultures and the direction of the reading [43]. There are also studies showing that right-handers tend to associate 'good' with 'right' and 'bad' with 'left' sides [44].

Participants identified important meaning differences between the diverse PGA formulations that might affect subsequent assessment, and some seem to prefer the formulation that asks for 'arthritis' and about 'today', mainly because it is easier. This is not surprising given the shorter time period recall required. However, this may be a major shortcoming of this PGA version. Patients come to see a health professional once every 3–6 months and ideally, it would be better to have an instrument that captures what is going on in a patient over a longer period, including crises such as RA flares.

Some participants, unaware of the purpose and use of PGA, gave a random number in the middle of the scale to avoid being near to zero. Some participants expressed doing this for fear of having their medication decreased. This observation supports previous findings that some patients, despite feeling an absence or reduction of symptoms and a 'sensation of return to normality', for strategic reasons, rarely use this end of the scale [45, 46].

Finally, participants were unaware how their PGA would inform the composite disease activity indices and thus influence treatment decisions. Providing a structured explanation on the purpose of PGA may help patients to see its importance and give it more thought before completing the measure, thus increasing its validity. Patients may also benefit from more education on how nurses and physicians use patient-reported disease measures [34, 47].

The change in the median PGA score and the remission rate after the intervention was not statistically significant. However, an 11% increase in the proportion of patients attaining near-remission (from 41 to 52%) immediately after the intervention suggests that this deserves attention and warrants further investigation.

This investigation has some limitations. First, cultural and educational factors, inherent to a single-centre study, can limit its generalizability. However, the results are generally in agreement with those of a recent report involving 300 patients with RA from the USA, 40% of which found PGA confusing, and emphasizing the relevance of lower health literacy and depressive symptoms in this confusion [47]. Second, as the youngest participant was 42 years old, this study does not embody the understanding of PGA of younger people with RA. Third, a relatively small sample was enrolled, and lastly, the effect of the structured explanation was tested on only one PGA formulation. Major strengths of this study were the use of three PGA formulations and the inclusion of patients with different disease activity states and not only patients who had an overall assessment divergent from the rheumatologist. Another strength is the use of a mixed-methods design and the involvement of three patient research partners.

In conclusion, this study found that patients have difficulties in understanding the meaning and the purpose of PGA. The tool had measurement difficulties arising from interpretation issues. The use of different versions of PGA as equivalent is problematic and can lead to different biases in the assessment of disease impact. Our study has shown that a structured explanation about PGA, given by a nurse and including its intended meaning and purpose, may help patients to complete this measure in a more meaningful way, and thus is likely to improve the validity of the assessment. This intervention has been shown to be feasible and further studies should test its effect using an adequately powered sample, multicentre and longitudinal design.

Acknowledgements

We wish to thank to all participants who accepted our invitation to participate in this study. We also wish to thank Professor Laure Gossec (UPMC University Paris 06, Paris, France) for her contribution to the design of this study and helpful comments on the early manuscript drafts.

Funding: No specific funding was received from any funding bodies in the public, commercial or not-for-profit sectors to carry out the work described in this manuscript.

Disclosure statement: The authors have declared no conflicts of interest.

Supplementary data

Supplementary data are available at *Rheumatology* online.

References

1 Nikiphorou E, Radner H, Chatzidionysiou K. Patient global assessment in measuring disease activity in rheumatoid

arthritis: a review of the literature. Arthritis Res Ther 2016;18:251.

2 Snyder E, Svetnik V, Tao P, Lines C, Herring WJ. Performance of the patient global impressions – severity scale as a self-reported patient assessment of insomnia severity. J Neurol Sci 2017;381:294.

3 Cooper TJ, Anker SD, Comin-Colet J *et al*. Relation of longitudinal changes in quality of life assessments to changes in functional capacity in patients with heart failure with and without anemia. Am J Cardiol 2016;117:1482–7.

4 Lam RW, Lamy FX, Danchenko N *et al*. Psychometric validation of the Perceived Deficits Questionnaire-Depression (PDQ-D) instrument in US and UK respondents with major depressive disorder. Neuropsychiatr Dis Treat 2018;14:2861–77.

5 Pascoe VL, Enamandram M, Corey KC *et al*. Using the physician global assessment in a clinical setting to measure and track patient outcomes. JAMA Dermatol 2015;151:375–81.

6 Adam B, Liebregts T, Saadat-Gilani K, Vinson B, Holtmann G. Validation of the gastrointestinal symptom score for the assessment of symptoms in patients with functional dyspepsia. Aliment Pharmacol Ther 2005;22:357–63.

7 Calabro JJ, Andelman SY, Caldwell JR *et al*. A multicenter trial of sulindac in osteoarthritis of the hip. Clin Pharmacol Ther 1977;22:358–63.

8 Meenan RF, Gertman PM, Mason JH. Measuring health status in arthritis. The arthritis impact measurement scales. Arthritis Rheum 1980;23:146–52.

9 van der Heijde DM, van't Hof MA, van Riel PL *et al*. Judging disease activity in clinical practice in rheumatoid arthritis: first step in the development of a disease activity score. Ann Rheum Dis 1990;49:916–20.

10 van der Heijde DM, van't Hof MA, van Riel PL *et al*. Validity of single variables and composite indices for measuring disease activity in rheumatoid arthritis. Ann Rheum Dis 1992;51:177–81.

11 Felson DT, Anderson JJ, Boers M *et al*. The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. The Committee on Outcome Measures in Rheumatoid Arthritis Clinical Trials. Arthritis Rheum 1993;36:729–40.

12 Gotzsche PC. Sensitivity of effect variables in rheumatoid arthritis: a meta-analysis of 130 placebo controlled NSAID trials. J Clin Epidemiol 1990;43:1313–8.

13 Bombardier C, Raboud J. A comparison of health-related quality-of-life measures for rheumatoid arthritis research. The Auranofin Cooperating Group. Control Clin Trials 1991;12:243s–56s.

14 Kilic L, Erden A, Bingham CO III, Gossec L, Kalyoncu U. The reporting of patient-reported outcomes in studies of patients with rheumatoid arthritis: a systematic review of 250 articles. J Rheumatol 2016;43:1300–5.

15 Kalyoncu U, Dougados M, Daures JP, Gossec L. Reporting of patient-reported outcomes in recent trials in rheumatoid arthritis: a systematic literature review. Ann Rheum Dis 2009;68:183–90.

16 Felson DT, Smolen JS, Wells G *et al*. American College of Rheumatology/European League against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Ann Rheum Dis 2011;70:404–13.

17 Smolen JS, Landewé R, Bijlsma J *et al*. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis 2017;76:960–77.

18 Smolen JS, Breedveld FC, Burmester GR *et al*. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. Ann Rheum Dis 2016;75:3–15.

19 van Tuyl LH, Boers M. Patient's global assessment of disease activity: what are we measuring? Arthritis Rheum 2012;64:2811–3.

20 Vermeer M, Kuper HH, van der Bijl AE *et al*. The provisional ACR/EULAR definition of remission in RA: a comment on the patient global assessment criterion. Rheumatology (Oxford) 2012;51:1076–80.

21 Studenic P, Smolen JS, Aletaha D. Near misses of ACR/EULAR criteria for remission: effects of patient global assessment in Boolean and index-based definitions. Ann Rheum Dis 2012;71:1702–5.

22 Masri KR, Shaver TS, Shahouri SH *et al*. Validity and reliability problems with patient global as a component of the ACR/EULAR remission criteria as used in clinical practice. J Rheumatol 2012;39:1139–45.

23 Ferreira RJO, Eugénio G, Ndosi M *et al*. Influence of the different ''patient global assessment'' formulations on disease activity score by different indices in rheumatoid arthritis. Clin Rheumatol 2018;37:1963–9.

24 Ferreira RJO, Duarte C, Ndosi M *et al*. Suppressing inflammation in rheumatoid arthritis: does patient global assessment blur the target? a practice-based call for a paradigm change. Arthritis Care Res (Hoboken) 2018;70:369–78.

25 Ferreira RJO, Dougados M, Kirwan J *et al*. Drivers of patient global assessment in patients with rheumatoid arthritis who are close to remission: an analysis of 1588 patients. Rheumatology (Oxford) 2017;56:1573–8.

26 Ferreira RJO, Duarte C, Ndosi M *et al*. The controversy of using PGA to define remission in RA. Nat Rev Rheumatol 2018;14:245.

27 van Tuyl LHD, Boers M. Rheumatoid arthritis: remission - keeping the patient experience front and centre. Nat Rev Rheumatol 2017;13:573–4.

28 Johnson RB, Onwuegbuzie AJ, Turner LA. Toward a definition of mixed methods research. J Mixed Methods Res 2007;1:112–33.

29 Zhang W, Creswell J. The use of ''mixing'' procedure of mixed methods in health services research. Med Care 2013;51:e51–7.

30 Arnett FC, Edworthy SM, Bloch DA *et al*. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315–24.

31 Aletaha D, Neogi T, Silman AJ *et al*. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2010;69:1580–8.

32 Thorne S, Kirkham SR, MacDonald-Emes J. Interpretive description: a noncategorical qualitative alternative for developing nursing knowledge. Res Nurs Health 1997;20:169–77.

33 Thorne S, Kirkham SR, O'Flynn-Magee K. The analytic challenge in interpretive description. Int J Qualitative Methods 2004;3:1–21.

34 Studenic P, Radner H, Smolen JS, Aletaha D. Discrepancies between patients and physicians in their perceptions of rheumatoid arthritis disease activity. Arthritis Rheum 2012;64:2814–23.

35 Gossec L, Dougados M, Rincheval N *et al*. Elaboration of the preliminary Rheumatoid Arthritis Impact of Disease (RAID) score: a EULAR initiative. Ann Rheum Dis 2009;68:1680–5.

36 Ward MM, Guthrie LC, Dasgupta A. Direct and indirect determinants of the patient global assessment in rheumatoid arthritis: differences by level of disease activity. Arthritis Care Res (Hoboken) 2017;69:323–9.

37 van Tuyl LH, Sadlonova M, Hewlett S *et al*. The patient perspective on absence of disease activity in rheumatoid arthritis: a survey to identify key domains of patient-perceived remission. Ann Rheum Dis 2017;76:855–61.

38 Walter MJM, van't Spijker A, Pasma A, Hazes JMW, Luime JJ. Focus group interviews reveal reasons for differences in the perception of disease activity in rheumatoid arthritis. Qual Life Res 2017;26:291–8.

39 Kvrgic Z, Asiedu GB, Crowson CS, Ridgeway JL, Davis JM III. ''Like No One Is Listening to Me'': a qualitative study of patient-provider discordance between global assessments of disease activity in rheumatoid arthritis. Arthritis Care Res (Hoboken) 2018;70:1439–47.

40 Challa DNV, Crowson CS, Davis JM III. The patient global assessment of disease activity in rheumatoid arthritis: identification of underlying latent factors. Rheumatol Ther 2017;4:201–8.

41 Ferreira RJO, Gossec L, Duarte C *et al*. The Portuguese Rheumatoid Arthritis Impact of Disease (RAID) score and its measurement equivalence in three countries: validation study using Rasch Models. Qual Life Res 2018;27:2909–21.

42 Van Tubergen A, Debats I, Ryser L *et al*. Use of a numerical rating scale as an answer modality in ankylosing spondylitis-specific questionnaires. Arthritis Rheum 2002;47:242–8.

43 Eldesouky D. Visual hierarchy and mind motion in advertising design. J Arts Human 2013;2:148–62.

44 Casasanto D, Chrysikou EG. When left is ''right''. Motor fluency shapes abstract concepts. Psychol Sci 2011;22:419–22.

45 van Tuyl LH, Hewlett S, Sadlonova M *et al*. The patient perspective on remission in rheumatoid arthritis: 'You've got limits, but you're back to being you again'. Ann Rheum Dis 2015;74:1004–10.

46 Inanc N, Yilmaz-Oner S, Can M, Sokka T, Direskeneli H. The role of depression, anxiety, fatigue, and fibromyalgia on the evaluation of the remission status in patients with rheumatoid arthritis. J Rheumatol 2014;41:1755–60.

47 Hirsh J, Wood P, Keniston A *et al*. Limited health literacy predicts patient confusion about patient global assessments of disease activity and rheumatoid arthritis model disease states. Arthritis Care Res (Hoboken) 2019;71:611–9.

Supplementary Table S1. Semi-structured interview guide

1. Could you please introduce yourself and tell me how long has your arthritis been diagnosed?

2. I would like you to carefully read and answer the question on this paper [a research assistant distribute PGA version 1]. After placing a mark in the line I would like you to reflect about what led you to give the score you gave. Please write down in the paper a few words that explain what was your understanding of the question. Please do not share with others before I ask for it.

3. Can you now share with others and me what you thought when you answered this question? You can also share what you consider when your rheumatologist asks you this question?

3a. Could you please give me an example?

3b. What do you mean by that?

4. Now I would like you to focus on this second question and do the same exercise (answer and then write the words of what you did understand). [PGA version 2]

5. Question 2 is repeated

6. Again, I want you to answer the question on the paper and then write a few words that explain your understanding of the question, if different from previous. [PGA version 3]

7. Question 3 is repeated

8. Could you tell me if you found any difference between these questions?

9. I will now present to you the 3 questions you just answered and discussed [One slide is projected on the wall]. Which one of the three questions do you prefer and why?

10. And now, seeing these 3 questions together, do you believe these 3 questions are asking the same things?

11. Do you think these questions are important for you or for your treatment? And if so, why?

12. Do you think the number you assigned to these questions can change or changes something regarding your treatment?

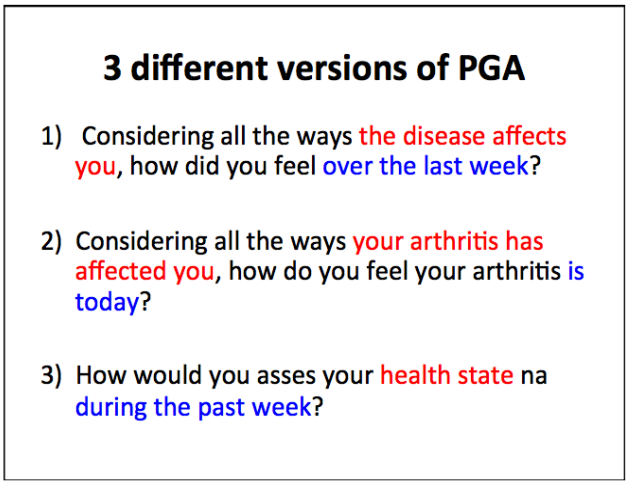
Lead investigator provides a brief structured explanation on PGA

13. Were you aware of this? Has anyone explained this to you before? How did this change the way you understood this question? Any doubts you would like to be clarified?

14. After this explanation, I would like you to answer, once again, one of the questions. [PGA version 2]. Did you answer somewhat differently from before?

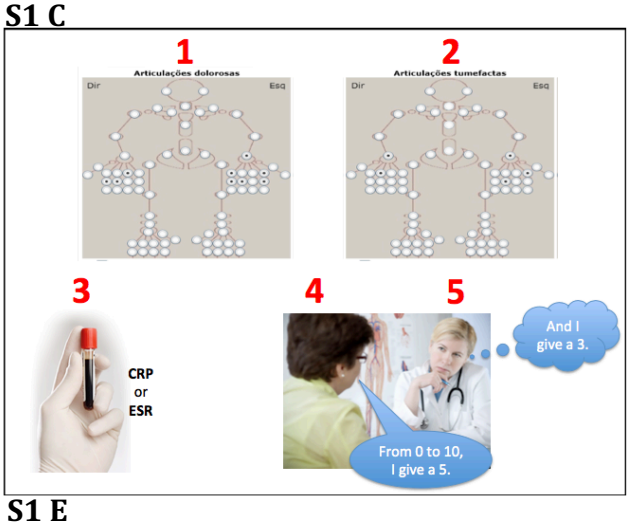
Supplementary Figure S1 - Visual aids used during the structured explanation about PGA

S1 A

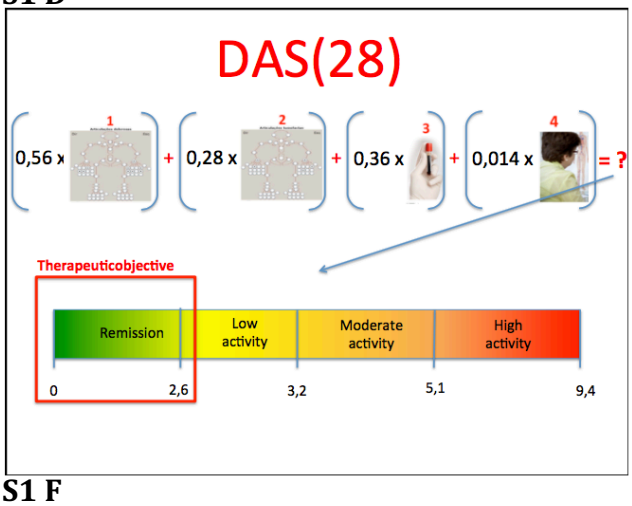


S1 B

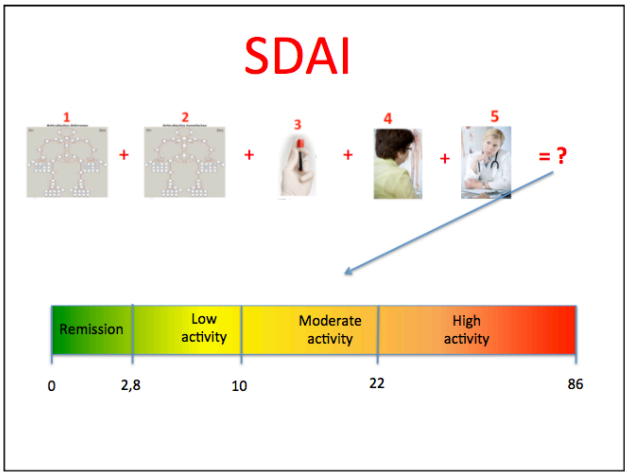
S1 C



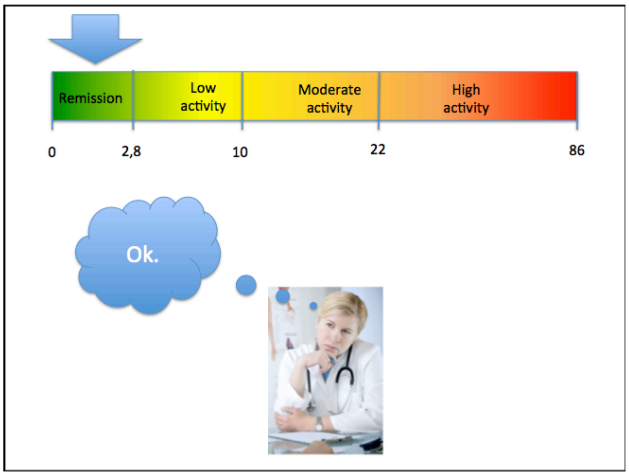
S1 D



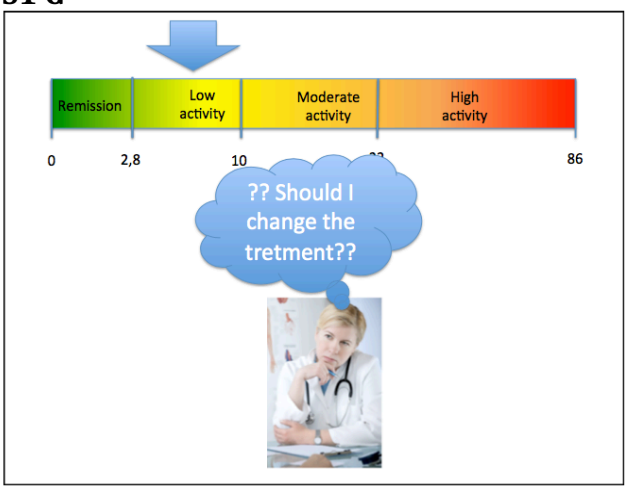
S1 E



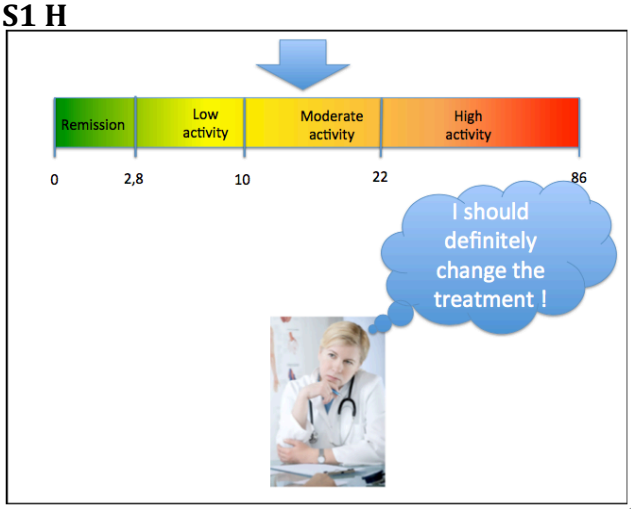
S1 F



S1 G



S1 H



Chapter III

UNDERSTANDING PGA AND ITS INFLUENCE ON REMISSION STATES IN RA

This chapter includes 3 published manuscripts and 1 published letter

Manuscript 3

Suppressing inflammation in rheumatoid arthritis: Does patient global assessment blur the target?

A practice-based call for a paradigm change.

Ferreira RJO, Duarte D, Ndosi M, de Wit M,
Gossec L*, da Silva JAP*

Arthritis Care Res (Hoboken). 2018; 70(3):369-378.

JOURNAL'S IMPACT FACTOR: 4.530

Number of external citations*: 11

Number of self-citations*: 10

CONFERENCES PRESENTATIONS/ABSTRACTS

Conference*:* EULAR Annual Congress 2016 (London, UK). Poster Tour.

Abstract*:* RJO Ferreira, C Duarte, C Silva, G Eugénio, M Ndosi, L Gossec, JAP da Silva (2016). THU0602 Patient Global Assessment in Rheumatoid Arthritis Conveys A Variable Blend of Disease Activity and Disease Impact: A Cross-Sectional Study with 311 Patients. *Ann Rheum Dis.* 75 (Suppl 2), 409-410

Journal's Impact Factor: 12.811

Number of external citations*: 0

Number of self-citations*: 0

OTHER SCIENTIFIC OUTPUTS

Thesis: Sousa JP (2015). [Patient Global Assessment of rheumatoid arthritis: How to interpret]. Master in Medicine. Faculty of Medicine, University of Coimbra, Coimbra, Portugal. Available at http://hdl.handle.net/10316/30901

- This thesis presented the results obtained from data of the first 101 patients.

Visualizations*: 612 (among the 20% most viewed)

Downloads*: 566 (among the 20% most downloaded)

Thesis: Baptista S (2015). [Discrepancy between patient and Physician in the assessment of rheumatoid arthritis disease activity]. Master in Medicine. Faculty of Medicine, University of Coimbra, Coimbra, Portugal. Available at http://hdl.handle.net/10316/30576

- This thesis presented the results obtained from data of the first 101 patients.

Visualizations*: 1005 (among the 5% most viewed)

Downloads*: 71

Thesis: Gonçalves S (2019). [Functional Capacity in the person with Rheumatoid Arthritis: associated factors and opportunities for Rehabilitation Nursing]. Master in Nursing Rehabilitation. Nursing School of Coimbra, Coimbra, Portugal. Available at http://web.esenfc.pt/?url=e8lVKOsA

- This thesis included an analysis of the association between remission states and physical function in the CoimbRA cohort.

Visualizations*: 11

Downloads*: 11

Views and News: This manuscript deserved a dedicated appraisal: Lilian H. D. van Tuyl and Maarten Boers. Remission keeping the patient experience front and centre. Nature Reviews Rheumatology doi:10.1038/nrrheum.2017.139 Published online 31 Aug 2017

Paper of the month: This manuscript was voted as the paper of the month (May 2018) by a young community of researchers in rheumatology (EMEUNET). Video interview available at https://youtu.be/oabm_YSoWg8

* until 30th august 2019

Arthritis Care & Research
Vol. 70, No. 3, March 2018, pp 369–378
DOI 10.1002/acr.23284

ORIGINAL ARTICLE

Suppressing Inflammation in Rheumatoid Arthritis: Does Patient Global Assessment Blur the Target? A Practice-Based Call for a Paradigm Change

RICARDO J. O. FERREIRA,[1] CÁTIA DUARTE,[2] MWIDIMI NDOSI,[3] MAARTEN DE WIT,[4] LAURE GOSSEC,[5] AND J. A. P. DA SILVA[2]

Objective. **In current management paradigms of rheumatoid arthritis (RA), patient global assessment (PGA) is crucial to decide whether a patient has attained remission (target) or needs reinforced therapy. We investigated whether the clinical and psychological determinants of PGA are appropriate to support this important role.**

Methods. **This was a cross-sectional, single-center study including consecutive ambulatory RA patients. Data collection comprised swollen 28-joint count (SJC28), tender 28-joint count (TJC28), C-reactive protein (CRP) level, PGA, pain, fatigue, function, anxiety, depression, happiness, personality traits, and comorbidities. Remission was categorized using American College of Rheumatology/European League Against Rheumatism Boolean-based criteria: remission, near-remission (only PGA >1), and nonremission. A binary definition without PGA (3v-remission) was also studied. Univariable and multivariable analyses were used to identify explanatory variables of PGA in each remission state.**

Results. **A total of 309 patients were included (remission 9.4%, near-remission 37.2%, and nonremission 53.4%). Patients in near-remission were indistinguishable from remission regarding disease activity, but described a disease impact similar to those in nonremission. In multivariable analyses, PGA in near-remission was explained ($R^2_{adjusted}$ = 0.50) by fatigue, pain, anxiety, and function. Fatigue and pain had no relationship with disease activity measures.**

Conclusion. **In RA, a consensually acceptable level of disease activity (SJC28, TJC28, and CRP level ≤1) does not equate to low disease impact: a large proportion of these patients are considered in nonremission solely due to PGA. PGA mainly reflects fatigue, pain, function, and psychological domains, which are inadequate to define the target for immunosuppressive therapy. This consideration suggests that clinical practice should be guided by 2 separate remission targets: inflammation (3v-remission) and disease impact.**

INTRODUCTION

The outlook of rheumatoid arthritis (RA) has improved remarkably over recent years, due to not only the development of new therapies but also novel treatment strategies (1). Among these, the treat-to-target recommendation (2,3) epitomizes the consensual concept that disease treatment should aim at achieving, as early and consistently as possible, a target level of remission, or at least low disease activity (3,4).

The provisional definition of remission in RA proposed jointly by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) (5), has been recommended for use in daily care of people with RA (3). This definition takes into consideration, in a Boolean format, swollen 28-joint count (SJC28), tender 28-joint count (TJC28), C-reactive protein (CRP) level, and patient global assessment (PGA). PGA weighs the same as the other components, which

[1]Ricardo J. O. Ferreira, RN, MSc: Centro Hospitalar e Universitário de Coimbra and Health Sciences Research Unit: Nursing, Coimbra, Portugal; [2]Cátia Duarte, MD, J. A. P. da Silva, MD, PhD: Centro Hospitalar e Universitário de Coimbra and University of Coimbra, Coimbra, Portugal; [3]Mwidimi Ndosi, RN, PhD: University of the West of England, Bristol, UK; [4]Maarten de Wit, PhD: Patient research partner, EULAR Standing Committee of People with Arthritis/Rheumatism in Europe, Zurich, Switzerland, and VU University Medical Centre, Amsterdam, The Netherlands; [5]Laure Gossec, MD, PhD: Sorbonne Universités, UPMC University Paris 06, Institut Pierre Louis d'Epidémiologie et de Santé Publique, GRC-UPMC 08 (EEMOIS), and AP-HP, Pitié-Salpetrière Hospital, Paris, France.

Drs. Gossec and da Silva contributed equally to this work.

Address correspondence to Ricardo J. O. Ferreira, RN, MSc, Serviço de Reumatologia, Consulta Externa, Piso 7, Centro Hospitalar Universitário de Coimbra, EPE, Avenida Dr. Bissaya Barreto, 3000-075 Coimbra, Portugal. E-mail: rferreira@reumahuc.org.

Submitted for publication March 3, 2017; accepted in revised form May 16, 2017.

Significance & Innovations

- In rheumatoid arthritis, patient global assessment (PGA) is frequently the sole criterion impeding patients from achieving the target of remission as defined by the American College of Rheumatology/European League Against Rheumatism Boolean-based criteria (4v-remission).
- A large proportion of patients with tight control of inflammation maintain a high PGA, and this level cannot be improved by further disease control.
- We therefore propose that an alternative definition of remission, based solely on joint counts and C-reactive protein level (3v-remission), is more appropriate to define the target for immunosuppressive therapy.
- Patients' perspective should remain core to disease assessment and management, but this perspective will be better served by more discriminative instruments than PGA.

are more closely related to disease activity (inflammation). The ethical and clinical imperative of incorporating patient-reported outcomes (PROs) in the decision process is indisputable, but reflection is needed on the best way to achieve this incorporation (6). The inclusion of PGA was mainly justified because it represents the patient's perspective and is responsive to treatment in clinical trials, discriminating between active and control intervention (5). However, considering that stopping progression of joint damage is one of the most important objectives of treatment in RA, a recent systematic review (7) concluded that only SJC and acute-phase reactants, but not PGA, were independent predictors of radiographic progression. Another point against PGA is its difficult interpretation (8–10). Until now, most studies suggested that PGA essentially reflects pain, function, and fatigue (10–15), which in turn have shown a variable correlation with inflammatory markers, in studies that did include psychosocial dimensions or perform multivariable analyses. Considerable percentages of PGA remain unexplained (>22%) (11), and few studies have explored its relationship with the underlying level of disease activity (10), or with the patient's psychological profile (10,16,17).

PGA has been identified as the main single factor impeding patients from reaching the state of remission (9,18–20). These patients represent 61–80% of all those who do not reach the ACR/EULAR Boolean remission due to a single parameter being >1, a state that has been designated as near-remission (18). Similar to patients in remission, they have a maximum of 1 SJC28, 1 TJC28, and 1 mg/dl CRP level. However, according to the ACR/EULAR definition, they will be considered in nonremission, because of PGA >1, thus becoming candidates for reinforced immunosuppressive therapy, following the current treatment guidelines (3,4).

The key clinical question we want to address is whether such patients require an increase in immunosuppressive therapy or would be best treated with alternative interventions directed at the causes of high-perceived disease impact. In order to answer this crucial clinical question it is essential to understand whether PGA conveys dimensions of the disease that are amenable to change by immunosuppressive therapy, especially in patients in near-remission.

The objectives of the present study were to: 1) understand how PGA correlates with a broad array of variables, including disease activity, comorbidities, psychological dimensions, and other measures of disease impact in people with RA; 2) determine whether these components of PGA variability change in different remission-state categories, especially in near-remission, thus impacting upon treat-to-target–driven decisions; 3) understand the explanatory variables for pain and fatigue; and 4) explore the adequacy of a remission definition without PGA (3v-remission) as a basis to define the target for immunosuppressive therapy, separating it from disease impact.

PARTICIPANTS AND METHODS

Study design, setting, and participants. This was an observational, cross-sectional study, performed in a single rheumatology outpatient department, in Portugal between September and December 2015. Consecutive adult patients satisfying current RA criteria (21,22) were invited to participate. Patients were excluded only if they were unable to respond to the questionnaires unaided. Patients were followed, monitored, and treated according to standard department guidelines. Ethical approval was granted by the University of Coimbra's Faculty of Medicine Ethics Committee (CE-037/2015), and all patients signed an informed consent form before the start of study procedures.

PGA. PGA was assessed using 2 different formulations: as stated in the ACR/EULAR definition of remission (5), "Considering all the ways your arthritis has affected you, how do you feel your arthritis is today?" and as stated in the Disease Activity Score using 28 joints (DAS28) definition (23), "How active was your arthritis during the past week?" Both formulations were presented as a 0–100-mm visual analog scale (VAS) as recommended, with their respective anchors of very well and very poor for the former, and not active at all and extremely active for the latter. Each formulation of PGA was presented in a single page of the questionnaire, interspersed with other PROs. The first formulation was used to define the ACR/EULAR remission status and was also taken as the dependent variable in all analyses.

Other variables. Patients responded to questionnaires including demographic data and the following PROs: pain (numerical rating scale [NRS], range 0–10), fatigue (NRS, range 0–10), function (Health Assessment Questionnaire [24]), anxiety and depression (Hospital Anxiety and Depression Scale [25]), and happiness, through the

Table 1. Demographic and clinical characteristics of rheumatoid arthritis patients (n = 309)*

Characteristic	Value
Demographic	
Age, years	59.5 ± 12.3
Female, no. (%)	253 (81.9)
Formal education, years†	7.4 ± 4.5
Disease characteristics	
Disease duration, years	12.0 ± 9.0
RF positive, no. (%)†	224 (74.2)
ACPA positive, no. (%)†	148 (69.8)
Erosions, no. (%)†	174 (69.6)
Comorbidities, no. (%)	
Fibromyalgia	52 (16.8)
Depression	66 (21.4)
Low back pain	79 (25.6)
Osteoporotic fractures	29 (9.4)
Osteoarthritis	181 (58.8)
Stroke	6 (1.9)
Current pharmacologic treatment, no. (%)†	
Synthetic disease-modifying drugs	275 (89.3)
Biologic agents	95 (30.8)
Glucocorticoids	212 (68.8)
Disease activity measure	
TJC28 (0–28)	1.4 ± 2.9
SJC28 (0–28)	1.4 ± 2.5
CRP, mg/dl	0.8 ± 1.4
DAS28-CRP (3v) (0–9.4)	2.5 ± 0.9
PhGA (VAS, 0–100)	13.4 ± 15.2
Disease activity status, no. (%)	
Remission‡	29 (9.4)
Near-remission§	115 (37.2)
Nonremission¶	165 (53.4)
3v-remission#	144 (46.6)
Disease impact measures**	
PGA (VAS, 0–100)	43.7 ± 26.7
Pain (NRS, 0–10)	4.9 ± 2.5
Fatigue (NRS, 0–10)	5.1 ± 2.7
HAQ (0–3)	1.1 ± 0.7
HADS-anxiety (0–21)†	8.4 ± 4.3
HADS-depression (0–21)†	7.3 ± 4.2
SHS (1–7)†	4.8 ± 1.3
TIPI (1–7)†	
Extraversion	4.2 ± 1.5
Agreeableness	5.7 ± 1.2
Conscientiousness	5.7 ± 1.3
Emotional stability	3.6 ± 1.5
Openness to experience	4.5 ± 1.4

* Values are the mean ± SD unless indicated otherwise. RF = rheumatoid factor; ACPA = anti-citrullinated antibody; TJC28 = tender 28-joint count; SJC28 = swollen 28-joint count; CRP = C-reactive protein; DAS28 = Disease Activity Score using 28 joints; PhGA = physician global assessment; VAS = visual analog scale; PGA = patient global assessment; NRS = numerical rating scale; HAQ = Health Assessment Questionnaire; HADS = Hospital Anxiety and Depression Scale; SHS = Subjective Happiness Scale; TIPI = Ten Item Personality Inventory.
† Percentages of patients with missing data were <2.5%, except for ACPA (31.4%) and erosions (19.1%).
‡ Remission (TJC28, SJC28, CRP level mg/dl, and PGA all ≤1).
§ Near-remission (TJC28, SJC28, and CRP level mg/dl all ≤1; PGA>1).
¶ Nonremission (TJC28 or SJC28 or CRP level mg/dl >1, irrespective of PGA value).
# 3v-remission (TJC28, SJC28, and CRP level mg/dl all ≤1; PGA not considered). It equates to merging remission and near-remission disease states.
** For all, except SHS and TIPI, higher scores correspond to worse outcomes.

Subjective Happiness Scale (26), a 4-item measure (7-point Likert scale). Personality was assessed with the Ten Item Personality Inventory (27), a brief measure of the Big-Five personality dimensions, each being scored as the mean of 2 items (7-point Likert scale). For both the latter measures, higher means correspond to more intense expression of the respective conditions.

The attending physician collected the following: year of diagnosis, rheumatoid factor and anti–citrullinated protein antibody (ACPA) status, presence/absence of erosions, TJC28, SJC28, CRP level, physician global assessment of disease activity (0–100-mm VAS), and current medications. Concomitant diagnoses were registered (fibromyalgia, depression, low back pain, osteoporotic fractures, osteoarthritis, and stroke), and the total number of comorbidities was computed. Patients completed the questionnaires unaided and before clinical consultation, to minimize the influence of the physician's assessment. Both patients with experience of using VAS/NRS (54.7%) and those with no previous experience were included.

Remission definitions. Patient's remission state was classified in 3 categories derived from the ACR/EULAR 2011 Boolean-based definition (5): remission (TJC28, SJC28, CRP level mg/dl, and PGA, all ≤1), near-remission (18) (TJC28, SJC28, and CRP level mg/dl ≤1; PGA>1), and nonremission (TJC28 or SJC28 or CRP level mg/dl >1). In addition, we explored the binary definition 3v-remission (28) (TJC28, SJC28, and CRP level mg/dl ≤1, where PGA is excluded from consideration). The DAS28-CRP (3v) considers TJC28, SJC28, and CRP level. The 3v version excludes the consideration of PGA, as required for the purposes of this study. We used the variant with CRP level, as the CRP level is more readily available in this medical center than the erythrocyte sedimentation rate.

Statistical methods. Quantitative data were expressed as means ± SDs and categorical data as frequencies and percentages. There was no imputation of missing data. Pearson's correlation coefficients between PGA and pain, fatigue, and all potentially explanatory continuous variables were calculated. Correlations were categorized as very good ($r \geq 0.60$), moderate ($r = 0.40$–0.59), and poor ($r < 0.40$) (29). Differences in variables between remission-state categories were tested in pairs using independent Student's *t*-test, with adjustment for relevant cofactors (analysis of covariance) where appropriate. Variables with *P* values less than 0.10 in the overall sample, and patients with full sets of data, were included in stepwise multivariable linear regression models (backward method) with PGA as a dependent variable. Two methods were used to prevent multicollinearity between explanatory variables in the multivariable models: assessment of bivariate correlations of possible explanatory variables prior to inclusion, defining $r < 0.80$ as the threshold for inclusion (30), and assessment of the variance inflation factor, assuming values <4 as acceptable (30). None of the variables was excluded based on these criteria. These multivariable linear regression analyses were performed for the overall sample. They were then repeated, using the same variables, for subsamples defined by the different disease remission states. Regarding

sample size, we established that a minimum of 10–15 patients per each explanatory variable should be recruited (total 200–300 patients) as recommended by Austin and Steyerberg (31). SPSS statistics software, version 20.0, was used for all analyses.

RESULTS

Patient characteristics. In total, 309 RA patients were included. Reasons for exclusion are shown in Supplementary Figure 1 (available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23284/abstract). Demographic and clinical characteristics of patients are shown in Table 1. A total of 79 patients (25.6%) had no comorbidities, and 5 accumulated a maximum of 5 comorbidities (data not shown). The mean ± SD DAS28-CRP (3v) was 2.5 ± 0.9 and for PGA was 43.7 ± 26.7. Regarding remission state, only 29 patients (9.4%) satisfied the ACR/EULAR criteria for remission. All remaining patients, in nonremission, were split according to the criteria described above, into near-remission 115 (37.2%) and nonremission 165 (53.4%). If PGA was not considered in the definition (3v-remission), the rate of patients classified in remission would increase from 9.4% to 46.6%.

Disease activity and disease impact across remission-state categories. The comparison between remission-state categories (Table 2) shows that near-remission is almost indistinguishable from remission in terms of disease activity measures, except for a slightly higher TJC28. Conversely, in terms of disease impact (PROs), near-remission is clearly distinct from remission but quite similar to nonremission. For instance, PGA in near-remission and nonremission is 10- and 11-fold, respectively, of the PGA reported by patients in remission.

When comparing all patients with TJC28, SJC28, and CRP level (mg/dl) ≤1 (3v-remission) versus those with at least 1 of these parameters >1 (3v-nonremission), the differences were equally clearcut in terms of disease activity (see Supplementary Table 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23284/abstract). Conversely, the disease impact measures largely overlap between these 2 categories (Table 2). Anxiety and depression were present at similar levels in near-remission and nonremission, but were significantly lower in remission. Happiness followed a similar pattern but did not reach statistical significance (Table 2).

PGA correlates across remission-state categories in univariable analyses. Overall, there were significant correlations between PGA and all continuous variables included, except for the personality domains agreeableness and conscientiousness (Table 3). These correlations were classifiable as good for pain, fatigue, and function, and as moderate for depression and anxiety. The remaining correlations were poor, including not only personality traits but also all variables representing disease activity. Looking at the correlations between PGA and explanatory variables by disease states, near-remission was similar to nonremission in showing significant correlation between PGA and all PROs, including subjective happiness. In remission, however, only fatigue and anxiety were significantly correlated with PGA. In both nonremission and remission, PGA was significantly correlated with CRP

Table 2. Adjusted comparison of disease activity measures and disease impact measures between remission-state categories in rheumatoid arthritis patients (n = 309)*

	A: remission (n = 29)	B: near-remission (n = 115)	C: nonremission (n = 165)	Adjusted *P*†		
				A vs. B	A vs. C	B vs. C
Disease activity measures						
TJC28 (0–28)	0.1 ± 0.3	0.3 ± 0.4	2.5 ± 3.7	0.028‡	0.005‡	< 0.001‡
SJC28 (0–28)	0.2 ± 0.4	0.2 ± 0.4	2.5 ± 3.0	0.449	< 0.001‡	< 0.001‡
CRP, mg/dl	0.2 ± 0.2	0.3 ± 0.2	1.3 ± 1.8	0.133	0.008‡	< 0.001‡
DAS28-CRP (3v) (0–9.4)	1.7 ± 0.3	1.8 ± 0.4	3.0 ± 0.8	0.165	< 0.001‡	< 0.001‡
PhGA (VAS, 0–100)	6.0 ± 10.2	6.0 ± 8.5	19.8 ± 16.6	0.770	< 0.001‡	< 0.001‡
Disease impact measures§						
PGA (VAS, 0–100)	4.5 ± 3.2	44.4 ± 22.3	50.0 ± 26.2	< 0.001‡	< 0.001‡	0.273
Pain (NRS, 0–10)	2.0 ± 2.1	4.7 ± 2.3	5.5 ± 2.3	< 0.001‡	< 0.001‡	0.019‡
Fatigue (NRS, 0–10)	1.8 ± 2.1	5.1 ± 2.3	5.7 ± 2.6	< 0.001‡	< 0.001‡	0.208
HAQ (0–3)	0.3 ± 0.5	1.0 ± 0.7	1.3 ± 0.7	< 0.001‡	< 0.001‡	< 0.001‡
HADS-anxiety (0–21)	5.3 ± 4.9	8.5 ± 3.9	8.9 ± 4.4	0.004‡	0.009‡	0.924
HADS-depression (0–21)	3.3 ± 3.4	7.0 ± 3.7	8.2 ± 4.3	< 0.001‡	< 0.001‡	0.091
SHS (1–7)	5.4 ± 1.2	4.9 ± 1.0	4.6 ± 1.4	0.154	0.065	0.072

* Values are the mean ± SD unless indicated otherwise. TJC28 = tender 28-joint count; SJC28 = swollen 28-joint count; CRP = C-reactive protein; DAS28 = Disease Activity Score using 28 joints; PhGA = physician global assessment; VAS = visual analog scale; PGA = patient global assessment; NRS = numerical rating scale; HAQ = Health Assessment Questionnaire; HADS = Hospital Anxiety and Depression Scale; SHS = Subjective Happiness Scale.
† One-way analysis of covariance test adjusted for age, sex, disease duration, years of formal education, and number of comorbidities.
‡ Statistically significant.
§ For all, except for SHS, higher scores correspond to worse outcomes.

Table 3. Pearson's correlation coefficients between PGA and other outcome measures according to remission-state categories in rheumatoid arthritis patients (n = 309)*

	All patients (n = 309)	Remission (n = 29)†	Near-remission (n = 115)‡	Nonremission (n = 165)§
Demographic, years				
Age	0.26¶	0.03	0.19#	0.26#
Disease duration	0.16#	−0.02	0.24#	0.10
Formal education	−0.34¶	−0.40#	−0.24#	−0.36¶
No. comorbidities (0–6)	0.36¶	0.19	0.34¶	0.32¶
Disease activity measures				
TJC28 (0–28)	0.32¶	0.39#	0.12	0.32¶
SJC28 (0–28)	0.16#	0.12	0.02	0.07
CRP, mg/dl	0.15#	0.20	0.09	0.08
DAS28-CRP (3v) (0–9.4)	0.36¶	0.47#	0.16	0.30¶
PhGA (VAS, 0–100)	0.22¶	0.04	0.12	0.13
Disease impact measure**				
Pain (NRS, 0–10)	0.67¶	0.10	0.59 ¶	0.64¶
Fatigue (NRS, 0–10)	0.67¶	0.65¶	0.62 ¶	0.61¶
HAQ (0–3)	0.65¶	0.22	0.49 ¶	0.67¶
HADS-anxiety (0–21)	0.53¶	0.43#	0.42 ¶	0.58¶
HADS-depression (0–21)	0.54¶	0.33	0.36 ¶	0.53¶
HSS (1–7)	−0.29¶	−0.05	−0.30#	−0.21#
TIPI (1–7)				
Extraversion	−0.17#	0.17	−0.09	−0.15
Agreeableness	−0.22	−0.27	0.08	−0.06
Conscientiousness	−0.11	−0.37	−0.04	−0.08
Emotional stability	−0.25¶	−0.13	−0.16	−0.24#
Openness to experience	−0.18#	−0.53#	−0.09	−0.16#

* Values are Pearson's correlation coefficient, where ≥0.60, 0.40–0.59, and <0.40 represent good, moderate, and poor correlations, respectively. PGA = patient global assessment; TJC28 = tender 28-joint count; SJC28 = swollen 28-joint count; CRP = C-reactive protein; DAS28 = Disease Activity Score using 28 joints; PhGA = physician global assessment; VAS = visual analog scale; NRS = numerical rating scale; HAQ = Health Assessment Questionnaire; HADS = Hospital Anxiety and Depression Scale; SHS = Subjective Happiness Scale; TIPI = Ten Item Personality Inventory.
† Remission (TJC28, SJC28, CRP level mg/dl, and PGA, all ≤1).
‡ Near-remission (TJC28, SJC28, and CRP level mg/dl, all ≤1; PGA>1).
§ Nonremission (TJC28 or SJC28 or CRP level mg/dl >1, irrespective of PGA value).
¶ $P < 0.001$.
# $P < 0.05$.
** For all except SHS and TIPI, higher values correspond to worse status.

level and DAS28-CRP (3v) but this was not the case in near-remission (Table 3).

The correlation between personality traits and PGA was largely absent or poor, except in the remission group, where openness to experience had moderate correlation with PGA. Overall, age, disease duration, and number of comorbidities were all significantly correlated with PGA in univariable analyses and, variably, in the remission-state categories. Years of formal education were inversely correlated with PGA in all groups (Table 3).

In the overall sample, a significantly higher PGA was observed in association with the presence of erosions and of each of the comorbidities considered, except osteoporotic fractures ($P = 0.055$). There were no significant differences in PGA by sex, rheumatoid factor and ACPA status, or familiarity with VAS/NRS (see Supplementary Table 2, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23284/abstract).

Correlates of PGA across remission states in multivariable analyses. The explanatory variables of PGA differed between the 3 remission-state categories. The best-fit model for near-remission ($R^2_{adjusted} = 0.50$), included fatigue, pain, anxiety, and function. None of the objective measures of disease activity was retained (Table 4). In nonremission, the model ($R^2_{adjusted} = 0.62$) retained function, pain, anxiety, SJC28, and years of formal education. Age, disease duration, depression, happiness, personality traits, number of comorbidities, and CRP level were not retained in the multivariable models for any of the remission-state categories.

Correlates of pain and fatigue. The origins of pain and fatigue, the most important correlates of PGA in near-remission patients, were statistically explored through univariable and multivariable analyses (see Supplementary Table 3, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23284/abstract). Patients in nonremission were also studied, for comparison. In the multivariable analyses (Table 5), pain was poorly explained in both near-remission ($R^2_{adjusted} = 0.51$) and nonremission ($R^2_{adjusted} = 0.54$). The best-fit models are different in the 2 remission states, including fatigue, anxiety, years of formal education, and extraversion for patients in near-remission, while for those in

Table 4. Multivariable linear regression models to explain PGA according to remission-state categories in rheumatoid arthritis patients (n = 292)*

	All patients (n = 292)		Remission (n = 28)†		Near-remission (n = 106)‡		Nonremission (n = 158)§	
	β stand.	*P*	β stand.	*P*	β stand.	*P*	β stand.	*P*
Pain	0.28	< 0.001¶	–	–	0.25	0.012¶	0.32	< 0.001¶
Fatigue	0.22	< 0.001¶	0.62	< 0.001¶	0.36	< 0.001¶	–	–
Function	0.26	< 0.001¶	–	–	0.14	0.078	0.35	< 0.001¶
HADS-anxiety	0.16	0.001¶	–	–	0.16	0.041¶	0.25	< 0.001¶
TJC28	–	–	0.33	0.024¶	–	–	–	–
SJC28	0.11	0.003¶	–	–	–	–	0.18	< 0.001¶
Formal education	−0.08	0.039¶	–	–	–	–	−0.12	0.030¶
R^2 adjusted	0.62		0.49		0.50		0.62	

* Variables included in all models: age, disease duration, formal education, no. of comorbidities, tender 28-joint count (TJC28), swollen 28-joint count (SJC28), C-reactive protein level, pain, fatigue, function, Hospital Anxiety and Depression Scale (HADS)-anxiety, HADS-depression, happiness, Ten Item Personality Inventory (TIPI) extraversion, TIPI conscientiousness, TIPI emotional stability, and TIPI openness to experience. PGA = patient global assessment; stand. = standardized.
† Remission (TJC28, SJC28, CRP mg/dl, and PGA, all ≤1).
‡ Near-remission (TJC28, SJC28, and CRP mg/dl, all ≤1; PGA>1).
§ Nonremission (TJC28 or SJC28 or CRP mg/dl >1, irrespective of PGA value).
¶ Statistically significant.

nonremission, the latter 2 are substituted by function and happiness. The correlates of fatigue in best-fit models include pain and function for both remission-state categories. In near-remission, 2 personality traits are also retained in the model, having a significant correlation with fatigue, whereas in nonremission, personality traits are dropped and anxiety is retained, increasing fatigue. None of the disease activity measures have a significant relationship with either pain or fatigue, irrespective of the remission-state category.

DISCUSSION

This is one of very few studies assessing PGA correlates across remission-state categories and the first using the Boolean-based definition for this purpose. The results

Table 5. Multivariable linear regression models to explain pain and fatigue in near-remission and nonremission-state categories in rheumatoid arthritis patients*

	Near-remission (n = 106)†		Nonremission (n = 158)‡	
	β stand.	*P*	β stand.	*P*
Pain				
Fatigue	0.64	< 0.001§	0.52	< 0.001§
Formal education	−0.16	< 0.026§	–	–
HADS-anxiety	0.14	0.065	0.13	0.061
TIPI extraversion	0.14	0.058	–	–
Function	–	–	0.25	< 0.001§
Happiness	–	–	0.14	0.029§
R^2 adjusted	0.51		0.54	
Fatigue				
Pain	0.58	< 0.001§	0.50	< 0.001§
Function	0.21	0.006§	0.19	0.006§
TIPI open to experience	−0.16	0.091	–	–
TIPI emotional stability	−0.13	0.050	–	–
HADS-anxiety	–	–	0.20	0.001§
R^2 adjusted	0.53		0.55	

* Variables included in all models: age, disease duration, formal education, no. of comorbidities, tender 28-joint count (TJC28), swollen 28-joint count (SJC28), C-reactive protein (CRP), pain or fatigue, function, Hospital Anxiety and Depression Scale (HADS)-anxiety, HADS-depression, happiness, Ten Item Personality Inventory (TIPI) extraversion, TIPI emotional stability, TIPI openness to experience. PGA = patient global assessment.
† Near-remission (TJC28, SJC28, and CRP mg/dl all ≤1; PGA>1).
‡ Nonremission (TJC28 or SJC28 or CRP mg/dl >1, irrespective of PGA value).
§ Statistically significant.

confirm previous observations (9,18–20) that a large percentage of RA patients in routine clinical practice miss the target of remission solely because of PGA. The percentage of near-remission observed (37.2%) was higher than reported before: 14.4–34.1% (9,15,17,18,20). These differences may be related to cultural issues (32,33), but the level of education and prevalence of emotional distress may also play a role. Whatever the reason, none of these percentages is negligible, as they could lead to different and potentially hazardous therapeutic decisions according to the current RA management recommendations. In this study, near-remission represents a 5-fold increase (from 9.4% to 46.6%) in the rate of remission.

PGA from patients in near-remission is not associated with disease activity but rather with fatigue, pain, anxiety, and function. Pain and fatigue, in turn, were correlated between them, and were influenced by anxiety, personality traits, and happiness, but bear no relationship with SJC28 or CRP level (Table 5). These observations are in close agreement with the findings reported by Ward et al (10).

In other studies (9–15,19), pain has been shown to be the best predictor of PGA, regardless of remission state. In the current study, pain was second to fatigue in explaining PGA in near-remission. Using a similar near-remission definition to ours, Studenic et al (18) demonstrated that higher pain levels lead to patients failing the ACR/EULAR Boolean-based definition only due to PGA. Ward et al (10) concluded that pain severity is the strongest determinant of PGA, not only directly, but also indirectly via deteriorated function, DAS28, and health distress.

In essence, the results of our study confirm and expand previous observations, and conjointly they underline the fact that in near-remission, PGA seems to convey and be driven by dimensions that are not obviously related to the inflammatory process and therefore cannot be expected to change because of reinforced immunosuppressive therapy. This fact does not imply that PGA is not correlated with disease activity, as argued to support the inclusion of this parameter in the ACR/EULAR definition of remission (5). In fact, PGA was also correlated, although just moderately, with DAS28-CRP (3v) in this study (Table 3). Interestingly, this correlation was true for the overall population ($r = 0.36$), for patients in nonremission ($r = 0.30$), and even for patients in remission ($r = 0.47$), despite the very low level of disease activity and PGA (≤1) in the latter group. However, this correlation was not the case in near-remission. PGA seems, therefore, to be in accordance with disease activity in both the remission and the nonremission group, but there is a clear mismatch between these dimensions in the near-remission group. These weak correlations between PGA and disease activity parameters reflect the fact that there is no meaningful relationship on the individual level. This finding does not mean, in any way, that the patient's perspective is not important. On the contrary, it is essential to care, as we discuss below.

The conclusions of this study need to be considered in the light of potential limitations. First, our population was recruited in a single center in Portugal, which may limit generalizability, as PGA and other PROs have been shown to vary across countries (33–35). The similarity of our findings with other studies is, however, rather reassuring in this respect. Second, the mean DAS28 in this sample was very low (mean ± SD 2.5 ± 0.9), reflecting a well-controlled disease cohort. Samples with higher mean DAS28 may have a lower percentage of near-remission patients. However, our analyses were performed by disease activity subgroups and these conclusions are probably applicable to other similar disease activity strata. Pharmacologic treatment used in our sample may also differ from other countries (36), but we believe that this difference does not affect the main results or the conclusions of this study. Third, its cross-sectional nature limits the ability to assess causality and progress over time. Fourth, the overall model explained only 62% of PGA. This limited number may be due to an inherent characteristic of the outcome or some relevant variables not being assessed, such as stiffness (13), work disability (37), or joints of the feet, although these were not a significant factor in the study by Studenic et al (18). Finally, analyses within the remission group are weakened by the small size of the group and the limited range of disease activity parameters and PGA allowed by the definition (all ≤1).

Conversely, the study presents a very robust and complete set of data, including domains that most physicians consider highly relevant but are seldom studied, like personality traits and emotional states. The sample included a wide diversity of age, disease activity, years of formal education, and previous experience with questionnaires and VAS, all of these being potentially relevant dimensions, rarely represented, with a range that allows proper statistical evaluation. Additionally, contrary to previous studies, we used the different formulations of PGA approved for each instrument, as these formulations may affect the results (38,39). Finally, our sample was also powered to allow strong statistical evaluation and was composed of unselected ambulatory patients.

The clinical implications of these observations are far-reaching. This study demonstrates that nonremission state as defined by the ACR/EULAR 4v Boolean concept brings together, due to a similar PGA, 2 different groups of patients in terms of disease activity: near-remission and nonremission (Table 2). This finding strongly supports the view that the target chosen to drive immunosuppressive therapy should not include PGA. In near-remission, the only targets that are appropriate for immunosuppressive therapy (SJC28, TJC28, and CRP level, i.e., 3v-remission) have already been achieved, but including PGA in the definition obscures that fact and puts the patient at risk of excessive treatment. A sharp target for any therapy should be defined by parameters amenable to change by that same therapy. This targeting is not the case for PGA regarding immunosuppression.

These observations call for a clear separation of the concepts of remission according to the objective of their use: control of inflammation (physicians' remission, as a target for immunosuppressive therapy) and control of disease impact (patients' remission, as target for overall management of the disease). The former offers a strong contribution but not a guarantee for the latter. The concept of 3v-remission provides the most appropriate definition for physician's remission, as it results in 2

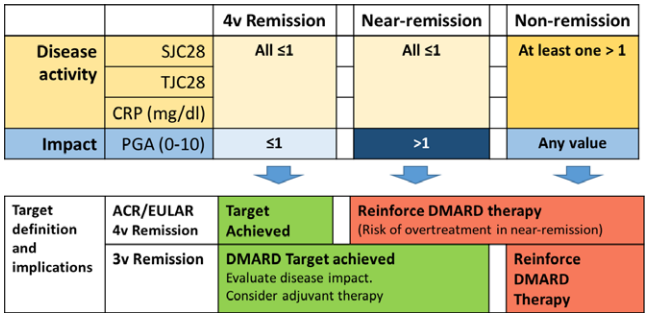


Figure 1. Proposed concept of remission based on 3v versus 4v Boolean-based definition in rheumatoid arthritis patients, and their therapeutic implications. SJC28 = swollen 28-joint count; TJC28 = tender 28-joint count; CRP = C-reactive protein; PGA = patient global assessment; ACR = American College of Rheumatology; EULAR = European League Against Rheumatism; DMARD = disease-modifying antirheumatic drug.

clearly separate and homogeneous groups of patients in terms of disease activity. For clarity, these concepts are shown in Figure 1.

The importance of patients' remission cannot and should not be overlooked, as controlling the impact of disease on patients' lives is the core objective of disease management. Given the relationship between disease activity and PGA described above, rheumatologists can be reassured that they will reduce disease impact in most patients, while controlling the disease process into remission. However, once TJC28, SJC28, and CRP level are close to or below 1 but PGA remains high, it is obviously not the time to increase immunosuppressive therapy, but rather to consider adjuvant therapies. Some adjuvant therapies have shown to improve several PGA-related variables. This improvement can be found with nonpharmacologic interventions, such as cognitive-behavioral therapy (40,41) and relaxation or biofeedback interventions (42) that address pain, functional disability, fatigue, sleep, depressive symptoms, anxiety, coping, self-efficacy, and even tender joints. Other nonpharmacologic interventions that have been shown to be effective are physical activity (43,44), occupational therapy (45), and patient education (46,47). These studies highlight the importance of a team approach to disease management as well as the importance of incorporating the patient's perspective in the overall treatment plan. PGA is not an appropriate instrument at this stage either, because it does not discriminate between the reasons for continued impact, which is essential to guide the selection of adjuvant therapy but can only be provided by discriminating instruments, such as the Rheumatoid Arthritis Impact of Disease score in its 7 domains (48).

Further investigation is needed to fully clarify these issues, including assessment of possible persistence of minimal inflammatory activity in patients in near remission and studies to determine whether a persistently high PGA in patients who are otherwise in remission has any impact upon long-term structural damage. The TJC28 may also be affected by concomitant diseases (e.g., fibromyalgia) and other factors such as psychological status. Factors associated with a high TJC28 when SJC28 and CRP level are ≤1 also deserve investigation in future studies. Additional evidence and guidance are needed on the origins and best management strategies for pain, fatigue, and other relevant domains of disease impact in RA.

In conclusion, this study demonstrates that in RA, control of inflammation does not equate to low disease impact. The impact of disease upon patients' lives is predominantly independent from the degree of inflammation, especially in near-remission. The results of this study suggest that the concepts of disease activity and disease impact should be addressed as separate domains. A definition of remission focused on inflammatory activity (physician's perspective, 3v-remission) is the most appropriate to serve as target for immunosuppressive therapy. The patient's perspective, i.e., disease impact, should be examined separately with more analytical measures than PGA, to guide efforts to alleviate impact beyond what is achieved through disease control.

ACKNOWLEDGMENTS

The authors thank Dr. C. Silva, G. Eugénio, S. Baptista, C. Medeiros, and J. P. Sousa for their help in data collection, as well as J. Silva, M. J. Salvador, S. Serra, M. Coutinho, and all other physicians from the Rheumatology Department at Coimbra, and C. Brás and E. Maia (department secretariat). We also thank Professor Helena Canhão (Nova Medical School, Lisbon) and Professor Loreto Carmona (InMusc, Madrid) for critically revising the manuscript for its intellectual content.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Ferreira had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Ferreira, Duarte, Ndosi, Gossec, da Silva.

Acquisition of data. Ferreira, Duarte, da Silva.

Analysis and interpretation of data. Ferreira, Duarte, Ndosi, de Wit, Gossec, da Silva.

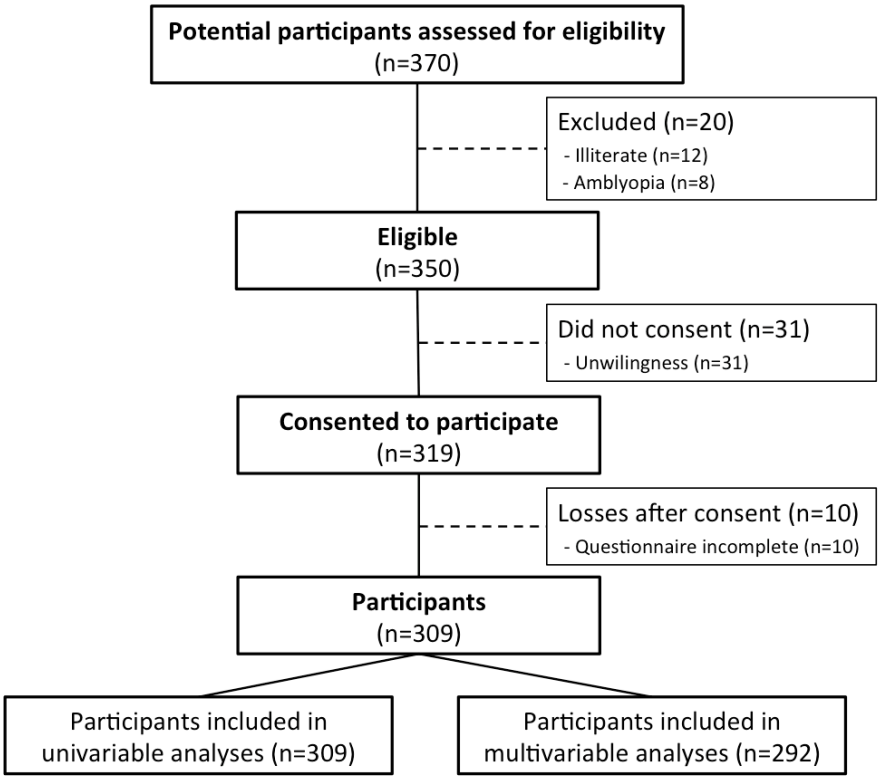
REFERENCES

1. Ramiro S, Machado P, Singh JA, Landewe RB, da Silva JA. Applying science in practice: the optimization of biological therapy in rheumatoid arthritis. Arthritis Res Ther 2010; 12:220.
2. Smolen JS, Breedveld FC, Burmester GR, Bykerk V, Dougados M, Emery P, et al. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. Ann Rheum Dis 2015;75:3–15.
3. Smolen JS, Landewe R, Breedveld FC, Buch M, Burmester G, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann Rheum Dis 2014;73:492–509.
4. Singh JA, Saag KG, Bridges SL Jr, Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Care Res (Hoboken) 2016;68:1–25.
5. Felson DT, Smolen JS, Wells G, Zhang B, van Tuyl LH, Funovits J, et al. American College of Rheumatology/

European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Arthritis Rheum 2011;63:573–86.
6. Miller D, Steele Gray C, Kuluski K, Cott C. Patient-centered care and patient-reported measures: let's look before we leap. Patient 2015;8:293–9.
7. Navarro-Compan V, Gherghe AM, Smolen JS, Aletaha D, Landewe R, van der Heijde D. Relationship between disease activity indices and their individual components and radiographic progression in RA: a systematic literature review. Rheumatology (Oxford) 2015;54:994–1007.
8. Van Tuyl LH, Boers M. Patient's global assessment of disease activity: what are we measuring? [editorial]. Arthritis Rheum 2012;64:2811–3.
9. Vermeer M, Kuper HH, van der Bijl AE, Baan H, Posthumus MD, Brus HL, et al. The provisional ACR/EULAR definition of remission in RA: a comment on the patient global assessment criterion. Rheumatology (Oxford) 2012;51:1076–80.
10. Ward MM, Guthrie LC, Dasgupta A. Direct and indirect determinants of the patient global assessment in rheumatoid arthritis: differences by level of disease activity. Arthritis Care Res (Hoboken) 2017;69:323–9.
11. Studenic P, Radner H, Smolen JS, Aletaha D. Discrepancies between patients and physicians in their perceptions of rheumatoid arthritis disease activity. Arthritis Rheum 2012;64:2814–23.
12. Egsmose EL, Madsen OR. Interplay between patient global assessment, pain, and fatigue and influence of other clinical disease activity measures in patients with active rheumatoid arthritis. Clin Rheumatol 2015;34:1187–94.
13. Khan NA, Spencer HJ, Abda E, Aggarwal A, Alten R, Ancuta C, et al. Determinants of discordance in patients' and physicians' rating of rheumatoid arthritis disease activity. Arthritis Care Res (Hoboken) 2012;64:206–14.
14. Ward MM, Guthrie LC, Alba MI. Measures of arthritis activity associated with patient-reported improvement in rheumatoid arthritis when assessed prospectively versus retrospectively. Arthritis Care Res (Hoboken) 2015;67:776–81.
15. Furu M, Hashimoto M, Ito H, Fujii T, Terao C, Yamakawa N, et al. Discordance and accordance between patient's and physician's assessments in rheumatoid arthritis. Scand J Rheumatol 2014;43:291–5.
16. Inanc N, Yilmaz-Oner S, Can M, Sokka T, Direskeneli H. The role of depression, anxiety, fatigue, and fibromyalgia on the evaluation of the remission status in patients with rheumatoid arthritis. J Rheumatol 2014;41:1755–60.
17. Ferreira RJ, Dougados M, Kirwan J, Duarte C, de Wit M, Soubrier M, et al. Drivers of patient global assessment in patients with rheumatoid arthritis who are close to remission: an analysis of 1588 patients. Rheumatology (Oxford) 2017;56:1573–8.
18. Studenic P, Smolen JS, Aletaha D. Near misses of ACR/EULAR criteria for remission: effects of patient global assessment in Boolean and index-based definitions. Ann Rheum Dis 2012;71:1702–5.
19. Masri KR, Shaver TS, Shahouri SH, Wang S, Anderson JD, Busch RE, et al. Validity and reliability problems with patient global as a component of the ACR/EULAR remission criteria as used in clinical practice. J Rheumatol 2012;39:1139–45.
20. Balogh E, Dias JM, Orr C, Mullan R, Harty L, FitzGerald O, et al. Comparison of remission criteria in a tumour necrosis factor inhibitor treated rheumatoid arthritis longitudinal cohort: patient global health is a confounder. Arthritis Res Ther 2013;15:R221.
21. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315–24.
22. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO III, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010;62:2569–81.
23. DAS28 form. URL: http://www.das-score.nl/das28/en/difference-between-the-das-and-das28/how-to-measure-the-das28/form-to-fill-in-the-das28.html.
24. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum 1980;23:137–45.
25. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361–70.
26. Lyubomirsky S, Lepper HS. A measure of subjective happiness: preliminary reliability and construct validation. Soc Indic Res 1999;46:137–55.
27. Gosling S, Rentfrow P, Swann W. A very brief measure of the Big-Five personality domains. J Res Pers 2003;37:504–28.
28. Svensson B, Andersson ML, Bala SV, Forslind K, Hafstrom I. Long-term sustained remission in a cohort study of patients with rheumatoid arthritis: choice of remission criteria. BMJ Open 2013;3:e003554.
29. Sharma AK. Textbook of correlations and regression. New Delhi: Discovery Publishing House; 2005.
30. Garson GD. Testing statistical assumption. Asheboro: Statistical Publishing Associates; 2012.
31. Austin PC, Steyerberg EW. The number of subjects per variable required in linear regression analyses. J Clin Epidemiol 2015;68:627–36.
32. Gvozdenovic E, Wolterbeek R, Allaart CF, Brenol C, Dougados M, Emery P, et al. Assessment of global disease activity in rheumatoid arthritis by patients and physicians: differences across countries in the METEOR database. J Clin Rheumatol 2015;21:349–54.
33. Putrik P, Ramiro S, Hifinger M, Keszei AP, Hmamouchi I, Dougados M, et al. In wealthier countries, patients perceive worse impact of the disease although they have lower objectively assessed disease activity: results from the cross-sectional COMORA study. Ann Rheum Dis 2015;75:715–20.
34. Gvozdenovic E, Koevoets R, Wolterbeek R, van der Heijde D, Huizinga TW, Allaart CF, et al. Assessment of global disease activity in RA patients monitored in the METEOR database: the patient's versus the rheumatologist's opinion. Clin Rheumatol 2014;33:461–6.
35. Hifinger M, Putrik P, Ramiro S, Keszei AP, Hmamouchi I, Dougados M, et al. In rheumatoid arthritis, country of residence has an important influence on fatigue: results from the multinational COMORA study. Rheumatology (Oxford) 2015;55:735–44.
36. Putrik P, Ramiro S, Kvien TK, Sokka T, Pavlova M, Uhlig T, et al. Inequities in access to biologic and synthetic DMARDs across 46 European countries. Ann Rheum Dis 2014;73:198–206.
37. Sokka T, Kautiainen H, Pincus T, Verstappen SM, Aggarwal A, Alten R, et al. Work disability remains a major problem in rheumatoid arthritis in the 2000s: data from 32 countries in the QUEST-RA study. Arthritis Res Ther 2010;12:R42.
38. French T, Hewlett S, Kirwan J, Sanderson T. Different wording of the patient global visual analogue scale (PG-VAS) affects rheumatoid arthritis patients' scoring and the overall disease activity score (DAS28): a cross-sectional study. Musculoskeletal Care 2013;11:229–37.
39. Dougados M, Ripert M, Hilliquin P, Fardellone P, Brocq O, Brault Y, et al. The influence of the definition of patient global assessment in assessment of disease activity according to the Disease Activity Score (DAS28) in rheumatoid arthritis. J Rheumatol 2011;38:2326–8.
40. Ferwerda M, van Beugen S, van Middendorp H, Spillekom-van Koulil S, Donders AR, Visser H, et al. A tailored-guided internet-based cognitive-behavioral intervention for patients with rheumatoid arthritis as an adjunct to standard rheumatological care: results of a randomized controlled trial. Pain 2017;158:868–78.
41. Hewlett S, Ambler N, Almeida C, Cliss A, Hammond A, Kitchen K, et al. Self-management of fatigue in rheumatoid arthritis: a randomised controlled trial of group cognitive-behavioural therapy. Ann Rheum Dis 2011;70:1060–7.

42. Astin JA, Beckner W, Soeken K, Hochberg MC, Berman B. Psychological interventions for rheumatoid arthritis: a meta-analysis of randomized controlled trials. Arthritis Rheum 2002;47:291–302.
43. Cramp F, Hewlett S, Almeida C, Kirwan JR, Choy EH, Chalder T, et al. Non-pharmacological interventions for fatigue in rheumatoid arthritis. Cochrane Database Syst Rev 2013;8:CD008322.
44. Feldthusen C, Dean E, Forsblad-d'Elia H, Mannerkorpi K. Effects of person-centered physical therapy on fatigue-related variables in persons with rheumatoid arthritis: a randomized controlled trial. Arch Phys Med Rehabil 2016;97: 26–36.
45. Siegel P, Tencza M, Apodaca B, Poole JL. Effectiveness of occupational therapy interventions for adults with rheumatoid arthritis: a systematic review. Am J Occup Ther 2017;71:7101180050p1–11.
46. Carandang K, Pyatak EA, Vigen CL. Systematic review of educational interventions for rheumatoid arthritis. Am J Occup Ther 2016;70:7006290020p1–12.
47. Ndosi M, Johnson D, Young T, Hardware B, Hill J, Hale C, et al. Effects of needs-based patient education on self-efficacy and health outcomes in people with rheumatoid arthritis: a multicentre, single blind, randomised controlled trial. Ann Rheum Dis 2016;75:1126–32.
48. Gossec L, Paternotte S, Aanerud GJ, Balanescu A, Boumpas DT, Carmona L, et al. Finalisation and validation of the rheumatoid arthritis impact of disease score, a patient-derived composite measure of impact of rheumatoid arthritis: a EULAR initiative. Ann Rheum Dis 2011;70:935–42.

Supplementary Figure S1 - Participants eligibility flow-chart



Supplementary Table S1 – Disease activity and disease impact measures for patients in 3v-remission and non-remission states

	3v-Remission# n=144	Non-Remission## n=165	Adjusted* p-values
Disease activity measures, mean (SD)			
TJC28 (0–28)	0.2 (0.4)	2.5 (3.7)	**<.001**
SJC28 (0–28)	0.2 (0.4)	2.5 (3.0)	**<.001**
CRP (mg/dl)	0.3 (0.2)	1.3 (1.8)	**<.001**
DAS28-CRP(3v) (0–9.4)	1.8 (0.4)	3.0 (0.8)	**<.001**
PhGA (VAS, 0-100)	6.0 (8.9)	19.8 (16.6)	**<.001**
Disease impact,¶ mean (SD)			
PGA (VAS, 0–100)	36.4 (25.6)	50.0 (26.2)	**<.001**
Pain (NRS, 0–10)	4.1 (2.5)	5.5 (2.3)	**<.001**
Fatigue (NRS, 0–10)	4.5 (2.6)	5.7 (2.6)	**.002**
HAQ (0–3),	0.8 (0.7)	1.3 (0.7)	**<.001**
HADS-Anxiety (0–21)	7.8 (4.2)	8.9 (4.4)	.422
HADS-Depression (0–21)	6.2 (3.9)	8.2 (4.3)	**.004**
SHS (1–7)	5.0 (1.1)	4.6 (1.4)	**<.001**

CRP = C-reactive protein; DAS28 = Disease Activity Score using 28 joints; HADS = Hospital Anxiety and Depression Scale; HAQ = Health Assessment Questionnaire; PGA = patient global assessment; PhGA = Physician global assessment; SHS = Subjective Happiness Scale; SJC28 = swollen joint counts using 28 joints; TJC28 = tender joint counts using 28 joints.
¶ For all, except SHS and TIPI, higher values correspond to worse status.
* One-way ANCOVA test adjusted for age, gender, disease duration, years of formal education, and number of comorbidities.
# 3v-Remission = TJC28, SJC28, and CRP mg/dl all ≤1; PGA not considered. It equates to merge "Remission" and " Near-remission" disease states.
Non-remission = TJC28 or SJC28 or CRP mg/dl >1, irrespective of PGA value.

Supplementary Table S2 – PGA by gender and clinical characteristics

Variable	Category	n	PGA Mean (SD)	t	p-value
Gender	Male	56	39.1 (23.5)	1.411	.159
	Female	253	44.7 (27.3)		
Familiarity with VAS/NRS	No	140	46.2 (26.3)	1.548	.123
	Yes	169	41.5 (30.0)		
RF	Negative	78	40.4 (27.7)	-1.223	.222
	Positive	224	44.7 (26.6)		
ACPA	Negative	64	43.8 (30.0)	0.465	.642
	Positive	148	41.8 (26.5)		
Erosions	Absent	76	38.0 (24.6)	-2.019	**.045**
	Present	174	45.4 (27.6)		
Fibromyalgia	No	257	42.2 (26.5)	-2.106	**.036**
	Yes	52	50.7 (27.0)		
Depression	No	242	40.1 (26.7)	-4.722	**<.001**
	Yes	66	57.1 (26.5)		
Low Back Pain	No	230	40.2 (26.3)	-3.932	**<.001**
	Yes	79	53.6 (25.4)		
Osteoporotic fractures	No	279	42.8 (26.2)	-1.927	.055
	Yes	29	52.8 (30.3)		
Osteoarthritis	No	127	35.1 (25.9)	-4.911	**<.001**
	Yes	181	49.8 (25.7)		

ACPA = anti-citrullinated antibody; NRS = numerical rating scale; PGA – Patient Global Assessment; RF = rheumatoid factor; VAS = visual analogue scale

Supplementary Table S3 – How fatigue and pain correlates with disease impact measures in near-remission and non-remission

	Fatigue Pearson's correlations, r_p (p-value)		Pain Pearson's Correlations, r_p (p-value)	
	Near-remission# n=114	Non-Remission## n=165	Near-remission# n=114	Non-Remission## n=165
Demographic				
Age (years)	.14	.29**	-.17	.26*
Disease duration (years)	.13	.02	.15	-.02
Formal Education (years)	-.13	-.30**	-.21*	-.29**
Nr. of comorbidities (0-6)	.27*	.41**	.25*	.37**
Disease activity measures				
TJC28 (0–28)	.07	.27*	.07	.28**
SJC28 (0–28)	.05	-.07	.05	-.06
CRP (mg/dl)	-.01	.07	.03	.15
DAS28-CRP(3v) (0–9.4)	.07	.21*	.09	.28**
Disease impact¶				
Pain (NRS: 0–10)	**.67****	**.71****	**--**	**--**
Fatigue (NRS: 0–10)	--	**--**	**.67****	**.71****
HAQ (0–3)	.47**	.57**	.41**	.58**
HADS-Anxiety (0–21)	.34**	.51**	.34**	.45**
HADS-Depression (0–21)	.34**	.53**	.35**	.46**
HSS (1–7)	-.24*	-.26**	-.27*	-.13*
TIPI (1-7)				
Extraversion	-.11	-.26*	-.01	-.24*
Agreeableness	.07	.04	.10	-.04
Conscientiousness	-.04	-.04	.03	.04
Emotional Stability	-.24*	-.34*	-.14	-.24*
Openness to Experiences	-.20*	-.10	-.09	.08

CRP = C-reactive protein DAS28 = Disease Activity Score using 28 joints; HADS = Hospital Anxiety and Depression Scale; HAQ = Health Assessment Questionnaire; SHS = Subjective Happiness Scale; SJC28 = swollen joint counts using 28 joints; TIPI = Ten Item Personality Inventory; TJC28 = tender joint counts using 28 joints. r_p = Pearson's correlation coefficient, where, ≥.60, .40-.59 and <.40 represent good, moderate and poor correlations respectively.

Near-remission = TJC28, SJC28, and CRP mg/dl all ≤1; PGA>1

Non-remission = TJC28 or SJC28 or CRP mg/dl >1, irrespective of PGA value

¶ For all, except SHS and TIPI, higher values correspond to worse status.

Manuscript 4

The controversy of using PGA to define remission in RA

Ferreira RJO, Duarte D, Ndosi M, de Wit M,
Gossec L, da Silva JAP

Nat Rev Rheumatol. 2018;14(4):245.

JOURNAL'S IMPACT FACTOR: 18.585

Number of external citations*: 1

Number of self-citations*: 4

* until 30th august 2019

LINK TO ORIGINAL ARTICLE
LINK TO AUTHOR'S REPLY

The controversy of using PGA to define remission in RA

Ricardo J. O. Ferreira, Cátia Duarte, Mwidimi Ndosi, Maarten de Wit, Laure Gossec and J. A. P. da Silva

We read with interest the commentary by van Tuyl and Boers (van Tuyl, L. H. D. & Boers, M. Remission — keeping the patient experience front and centre. *Nat. Rev. Rheumatol.* **13**, 573–574 (2017))[1] referring to our paper on the role of patient global assessment (PGA) in the definition of remission in rheumatoid arthritis (RA)[2]. However, we cannot agree with their interpretation that by suggesting to remove the PGA from the ACR/EULAR remission definition we are "calling for a paradigm change that limits the responsibility of the rheumatologist to prescribing immunosuppressive therapy," or that our proposal is "taking away the incentive to improve RA care by removing the patient's perspective from the remission criteria."[1]

Nothing could be further from the interpretation we made of our own data and from our proposals. What we actually proposed is that the management of RA should be guided by two separate targets: a measure of inflammatory activity (physician's perspective) and a measure of disease impact (patient's perspective).

We advocate that 3v-remission (defined as swollen and tender 28-joint counts and C-reactive protein in mg/dl all ≤1) is the most appropriate target for immunosuppressive therapy given that PGA has been shown to have no more than a weak correlation with disease activity, and is at least as much linked to personality and emotional aspects, which are not amenable to change by immunosuppressive therapy.

Achieving 3v-remission is a decisive step towards achieving good patient outcomes but does not guarantee the total abrogation of disease impact. In fact, the percentage of patients with RA who are missing remission solely because of a high PGA score is greater than the percentage who achieve full remission[2,3]. To further assist such patients, physicians ought to consider adjuvant interventions instead of reinforced immunosuppression.

For these reasons, a measure of disease impact should be part of the recommended treatment targets in RA management. This measure should be examined separately from inflammatory activity and include more analytical measures than PGA, in order to guide efforts to alleviate impact beyond what is achieved through control of inflammation. We suggest that the Rheumatoid Arthritis Impact of Disease (RAID) score, using its seven domains as separate items, is ideally suited for this purpose. The RAID score was developed in close cooperation with patients from various countries[4].

Our views were summarized in the abstract: "PGA mainly reflects fatigue, pain, function, and psychological domains, which are inadequate to define the target for immunosuppressive therapy. This consideration suggests that clinical practice should be guided by two separate remission targets: inflammation (3v-remission) and disease impact."[2]

In summary, we do not propose to "limit the responsibility of the rheumatologist to prescribing immunosuppressive therapy"[1], but rather we want to highlight the rheumatologist´s and multidisciplinary team's responsibility to assess and manage disease impact. The appropriateness of these proposals will be further scrutinized by clarifying whether high PGA in patients otherwise in remission is associated with subclinical inflammation and whether full remission is a better predictor than 3v-remission (without PGA) of a long-term good radiological outcome[5]. Both investigations are underway.

[1]*Rheumatology Department, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal.*

[2]*Health Sciences Research Unit: Nursing (UICiSA:E), Coimbra, Portugal.*

[3]*Clínica Universitária de Reumatologia, Faculty of Medicine, University of Coimbra, Coimbra, Portugal.*

[4]*Department of Nursing and Midwifery, Faculty of Health and Applied Sciences, University of the West of England, Bristol, UK.*

[5]*Patient research partner, EULAR standing committee of People with Arthritis/Rheumatism in Europe (PARE), Zurich, Switzerland.*

[6]*Department of Medical Humanities, VU University Medical Centre, Amsterdam, Netherlands.*

[7]*Sorbonne Universités, UPMC Univ. Paris 06, Institut Pierre Louis d'Epidémiologie et de Santé Publique, GRC-UPMC 08 (EEMOIS), Paris, France.*

[8]*Rheumatology Department, AP-HP, Pitié-Salpetrière Hospital, Paris, France*

**e-mail: rferreira@reumahuc.org*

doi:10.1038/nrrheum.2018.35
Published online 21 Mar 2018

1. van Tuyl, L. H. D. & Boers, M. Remission — keeping the patient experience front and centre. *Nat. Rev. Rheumatol.* **13**, 573–574 (2017).
2. Ferreira, R. J. O. et al. Suppressing inflammation in rheumatoid arthritis: does patient global assessment blur the target? A practice-based call for a paradigm change. *Arthritis Care Res.* https://doi.org/10.1002/acr.23284 (2017).
3. Ferreira, R. J. O. et al. Drivers of patient global assessment in patients with rheumatoid arthritis who are close to remission: an analysis of 1588 patients. *Rheumatology*. (*Oxford).* **56**, 1573–1578 (2017).
4. Gossec, L. et al. Finalisation and validation of the rheumatoid arthritis impact of disease score, a patient-derived composite measure of impact of rheumatoid arthritis: a EULAR initiative. *Ann. Rheum. Dis.* **70**, 935–942 (2011).
5. Ferreira, R. J. O. et al. The impact of patient global assessment in the definition of remission as a predictor of long-term radiographic damage in patients with rheumatoid arthritis: protocol for an individual patient data meta-analysis. *Acta Rheumatol. Port.* http://www.actareumatologica.pt/article_abstract.php?id=1197 (2018).

Competing interests
The authors declare no competing interests.

Author contributions
R.J.O.F. and J.A.P.S researched data for the article and wrote the article. R.J.O.F., C.D., M.N., L.X., M.W., L.G. and J.A.P.S. made substantial contributions to discussion of its content and reviewed and/or edited the manuscript before submission.

Manuscript 5

Drivers of patient global assessment in patients with rheumatoid arthritis who are close to remission: an analysis of 1588 patients.

Ferreira RJO, Dougados M, Kirwan JK, Duarte D, de Wit M,
Soubrier M, Fautrel B, Kvien TK, da Silva JAP*, Gossec L*
on on behalf of the CoimbRA investigators, RAID investigators and COMEDRA investigators

Rheumatology (Oxford). 2017;56(9):1573-1578.

JOURNAL'S IMPACT FACTOR: 5.245

Number of external citations*: 12

Number of self-citations*: 11

CONFERENCES PRESENTATIONS/ABSTRACTS

This paper resulted from secondary analysis of data from different studies. Different presentations in international conferences were accepted but for the primary studies.

* until 30th august 2019

RHEUMATOLOGY

Rheumatology 2017;56:1573–1578
doi:10.1093/rheumatology/kex211
Advance Access publication 13 June 2017

Concise report

Drivers of patient global assessment in patients with rheumatoid arthritis who are close to remission: an analysis of 1588 patients

Ricardo J. O. Ferreira[1,2], Maxime Dougados[3,4,5], John R. Kirwan[6], Cátia Duarte[7,8], Maarten de Wit[9,10], Martin Soubrier[11], Bruno Fautrel[12,13,14], Tore K. Kvien[15], José A. P. da Silva[7,8,*] and Laure Gossec[12,13,*], on behalf of the CoimbRA investigators, RAID investigators and COMEDRA investigators

Abstract

Objectives. ACR/EULAR Boolean remission in RA is frequently not obtained solely due to a patient global assessment (PGA) >1/10 (a condition often designated as near-remission). This study aimed to assess which domains of impact could explain an elevated PGA in near-remission patients.

Methods. We performed an ancillary analysis of data from three cross-sectional studies in patients with established RA. Three disease activity states were defined: remission (tender and swollen joint counts, CRP and PGA all ⩽1), near-remission (tender and swollen joint counts, and CRP are all ⩽1 but PGA >1) and non-remission. Physical and psychological domains were assessed using the RA Impact of Disease 0–10 (numeric rating scale) as explanatory factors of PGA. Univariable and multivariable linear regression analyses were performed to explain PGA.

Results. A total of 1588 patients (79.1% females) were analysed. The mean disease duration was 13.0 years (S.D. 9.8) and the 28-joint DAS with four variables was 3.2 (S.D. 1.4). Near-remission [mean PGA 3.6 (S.D. 1.9)] was more frequent (19.1%) than remission (12.3%). Scores of RA Impact of Disease domains were similar in near-remission and non-remission patients. In near-remission, PGA was explained ($R^2_{adjusted} = 0.55$) by pain ($\beta = 0.29$), function ($\beta = 0.23$), physical well-being ($\beta = 0.19$) and fatigue ($\beta = 0.15$).

Conclusion. Near-remission was more frequent than remission. These patients, despite having no signs of significant inflammation, report an impact of disease similar to the non-remission patients. PGA in near-remission seems to be driven by physical rather than psychological domains. Selecting the best therapy for these patients requires a better understanding of the meaning of PGA, both globally and in individual patients.

Key words: rheumatoid arthritis, patient global assessment, patient reported outcomes, disease activity, remission, near-remission, psychological distress, psychological factors, outcomes, disease impact

CLINICAL SCIENCE

[1]Department of Rheumatology, Centro Hospitalar e Universitário de Coimbra, [2]Health Sciences Research Unit: Nursing (UICiSA:E), Nursing School of Coimbra (ESEnfC), Coimbra, Portugal, [3]Faculty of Medicine, Paris Descartes University, [4]Department of Rheumatology, AP-HP, Hôpital Cochin, [5]INSERM (U1153), Clinical Epidemiology and Biostatistics, PRES Sorbonne Paris-Cité, Paris, France, [6]Academic Rheumatology Unit, Bristol Royal Infirmary, University of Bristol, Bristol, UK, [7]Department of Rheumatology, Centro Hospitalar e Universitário de Coimbra, [8]Clínica Universitária de Reumatologia, Faculty of Medicine, University of Coimbra, Coimbra, Portugal, [9]Patient Research Partner, EULAR Standing Committee of People with Arthritis/Rheumatism in Europe (PARE), Zurich, Switzerland, [10]Department of Medical Humanities, VU University Medical Centre, Amsterdam, The Netherlands, [11]Department of Rheumatology, CHU Clermont-Ferrand, Clermont-Ferrand, [12]Faculty of Medicine, UPMC University Paris 06, GRC-UPMC 08 (EEMOIS), [13]Department of Rheumatology, AP-HP, Pitié Salpêtrière Hospital, Paris, [14]CRI IMIDIATE, French Clinical Research Infrastructure Network, Toulouse, France and [15]Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway

Submitted 12 October 2016; revised version accepted 25 April 2017

*José A. P. da Silva and Laure Gossec contributed equally to this study.

Correspondence to: Ricardo Jorge de Oliveira Ferreira, Serviço de Reumatologia, Consulta Externa, Piso 7, Centro Hospitalar Universitário de Coimbra, EPE, Avenida Dr. Bissaya Barreto, 3000-075 Coimbra, Portugal.
E-mail: ferreira.rjo@gmail.com

Rheumatology key messages

- One-third of RA patients fail to reach remission solely because of patient global assessment (near-remission).
- In near-remission RA patients, significant disease impact may persist despite the absence of signs of inflammation.
- High patient global assessment in near-remission reflects both psychological and physical aspects of the disease impact of RA.

Introduction

Disease remission (or at least low disease activity) is the therapeutic target for patients with RA in current treatment recommendations [1, 2]. Remission is defined according to the ACR/EULAR criteria [3], which in the Boolean-based definition require that the 28 tender joint count (TJC28), 28 swollen joint count (SJC28), CRP (mg/dl) and patient global assessment (PGA; 0–10 scale) are all $\leqslant 1$.

The condition where patients fail to reach remission solely because of PGA has been designated as near-remission [4]. These patients have no signs of significant joint inflammation since joint counts and CRP are $\leqslant 1$, but they evaluate their disease (using PGA) as $> 1/10$. In published studies, 21–31% of RA patients were in near-remission [4–6]. Following current treatment recommendations [1, 2], this state of near-remission could justify reinforcement of immunosuppressive therapy. However, this may not be the best choice if the reason for not achieving remission is not inflammatory activity. In these cases, adjuvant therapies such as analgesics, anti-depressants or self-management programs might be more appropriate. To select the best intervention in such cases, it is essential to understand why patients without signs of significant inflammatory activity do not achieve a PGA $\leqslant 1$.

In RA patients, PGA appears to be influenced by not only RA disease activity, but also by sociodemographic features, country/culture, psychological factors and comorbidities, with emphasis on FM [7]. However, no data are available on the meaning of PGA in the specific condition of near-remission.

The aims of this study were to assess which domains of impact may explain the elevated PGA in near-remission patients and to assess which domains of health better discriminate between disease activity states.

Methods

Study design and setting

This was an ancillary analysis of three studies of patients with established RA: baseline data from the RA Impact of Disease (RAID) elaboration database [8], an international (12 European countries) observational study in 2008–09; baseline data from COMorbidities, EDucation in Rheumatoid Arthritis (COMEDRA) trial [9], a French multicentre clinical trial in 2011; and the Coimbra RA cohort (CoimbRA), a Portuguese, cross-sectional observational study in 2015 [10].

Participants

In all three studies consecutive adult patients were included if they had definite RA (ACR 1987 revised criteria or ACR/EULAR 2010 classification criteria) and were able to complete questionnaires. For COMEDRA, additional inclusion criteria were age <80 years, stable disease (for at least 3 months) and having no planned surgery in the 6 months following the study baseline. Written consent was obtained according to the Declaration of Helsinki for all studies, as well as approval from ethical committees, as previously reported [8–10]. Additional approval for this ancillary study was not required. Here, patients were analysed if they had RAID [8] and remission components available [3].

PGA

PGA was assessed in the three studies using the same formulation [3]—considering all the ways your arthritis has affected you, how do you feel your arthritis is today?—using either a 0–100 visual analogue scale or a 0–10 numeric rating scale (in COMEDRA).

Remission definitions

Four different Boolean-based concepts of remission were used in this study: the ACR/EULAR Boolean remission [TJC28, SJC28, CRP (mg/dl) and PGA, all $\leqslant 1$] [3]; near-remission [TJC28, SJC28 and CRP (mg/dl) all $\leqslant 1$ and PGA >1]; non-remission [TJC28 or SJC28 or CRP (mg/dl) >1, irrespective of PGA] and three-variable (3v) remission [11] [TJC28, SJC28 and CRP (mg/dl) all $\leqslant 1$; PGA excluded from consideration].

Explanatory factors of PGA

The seven domains of the RAID score [8] were used as possible factors to explain PGA: that is, physical (pain, function and physical well-being), psychological (emotional well-being and coping/self-efficacy) and mixed domains (fatigue and sleep) [12]. Each domain is assessed by a numeric rating scale, ranging from 0 (no impact) to 10 (high impact).

Other data collection

Age, gender, disease duration, current biologic agent (yes/no), HAQ, physician's global assessment and 28-joint DAS with 4 variables (DAS28-4v) were also assessed for patient's characterization.

Statistical analyses

Descriptive analyses, Student's *t*-test comparing disease activity states and Hedges' g for effect size (ES) were performed using SPSS Statistics version 20.0 software (IBM, Armonk, NY, USA). The ES assessed the discriminant capacity of impact domains to distinguish the disease activity states. To determine the drivers of PGA in near-

remission patients, univariable (Pearson's correlation coefficient) and multivariable analyses (linear regression, backward method) were used.

Results

Patient characteristics

The evaluable population comprised 1588 patients (RAID = 348, COMEDRA = 936, CoimbRA = 304) who presented with typical established RA with long disease duration (Table 1). Patients from COMEDRA and RAID were often treated with biologic disease-modifying drugs (74.7% and 50.0%, respectively). Disease activity was, on average, low in COMEDRA and in CoimbRA and moderate in RAID (Table 1). All aspects of disease impact presented mean values of ~3.5 on 0–10 scales, except for fatigue [mean 4.3 (S.D. 2.8)], where higher numbers reflect worst status (Table 1).

Remission rates and PGA cut-offs

ACR/EULAR Boolean-based remission was achieved by only 195 (12.3%) patients (6.0% in RAID, 15.6% in COMEDRA and 9.2% in CoimbRA). Overall, 303 (19.1%) patients were in near-remission (14.4% in RAID, 14.6% in COMEDRA and 38.2% in CoimbRA). Near-remission was at least as frequent as remission (COMEDRA) and up to four times more frequent (CoimbRA). Overall, 498 (31.4%) patients had no signs of inflammation as currently assessed, that is, they were in 3v remission (Table 1).

In the near-remission group ($n = 303$), the mean PGA was considerably above the ACR/EULAR Boolean cut-off of $\leqslant 1$ [mean 3.6 (S.D. 1.9)], with 70.3 and 43.9% of patients having a score >2 and >3, respectively (supplementary Fig. S1, available at *Rheumatology* Online).

Impact domains according to disease activity states

Table 2 presents disease impact domains according to remission status. In non-remission patients ($n = 1090$), all the disease impact domains had mean values >3.4, with coping, sleep and emotional well-being scoring lower/better than physical domains. Conversely, in remission patients ($n = 195$), only fatigue (mean 1.3) and physical well-being (mean 1.1) presented means >1.

Mean values of disease impact measures were very similar for patients in near-remission and in non-remission, except ($P < 0.05$) for the pain, physical well-being and function domains (Table 2). Mean scores of disease impact measures were markedly different between patients in remission and those in near-remission ($P < 0.001$ in all cases) (Table 2). These two groups are brought together under the concept of 3v remission, whose values of disease impact are, as expected, between the two (Table 2 and supplementary Table S1, available at *Rheumatology* Online).

Table 1 Demographic and clinical characteristics of 1588 RA patients

Characteristics	RAID (n = 348)	COMEDRA (n = 936)	CoimbRA (n = 304)	All patients (n = 1588)
Age[a], mean (S.D.), years	55.9 (12.9)	57.6 (11.1)	59.4 (12.4)	57.6 (11.8)
Female gender[a], n (%)	262 (75.9)	742 (79.3)	249 (81.9)	1253 (79.1)
Disease duration[a], mean (S.D.), years	12.7 (10.6)	13.5 (9.8)	11.9 (9.0)	13.0 (9.8)
Current biologic agents, n (%)	174 (50.0)	699 (74.7)	95 (31.3)	968 (61.0)
HAQ[a] (0–3), mean (S.D.)	1.18 (0.76)	0.40 (0.46)	1.09 (0.74)	0.70 (0.70)
TJC28 (0–28), mean (S.D.)	5.5 (6.5)	3.3 (4.2)	1.4 (2.9)	3.4 (4.8)
SJC28 (0–28), mean (S.D.)	3.7 (4.5)	2.2 (3.1)	1.4 (2.5)	2.4 (3.4)
CRP, mean (S.D.), mg/dl	1.1 (1.6)	0.5 (1.3)	0.8 (1.4)	0.7 (1.4)
PhGA[a] (0–10), mean (S.D.)	3.4 (2.4)	2.3 (1.7)	1.3 (1.5)	2.4 (2.0)
DAS28-ESR (4v)[a] (0–9.4), mean (S.D.)	4.0 (1.6)	3.1 (1.3)	2.8 (1.2)	3.2 (1.4)
Disease activity states, n (%)				
3v remission[b]	71 (20.4)	283 (30.2)	144 (47.4)	498 (31.4)
Remission[c]	21 (6.0)	146 (15.6)	28 (9.2)	195 (12.3)
Near-remission[d]	50 (14.4)	137 (14.6)	116 (38.2)	303 (19.1)
Non-remission	277 (79.6)	653 (69.8)	160 (52.6)	1090 (68.6)
PGA (0–10), mean (S.D.)	4.2 (2.5)	2.9 (2.1)	4.4 (2.7)	3.5 (2.4)
Pain (0–10), mean (S.D.)	4.7 (2.7)	3.0 (2.2)	4.9 (2.5)	3.7 (2.5)
Function (0–10), mean (S.D.)	4.5 (2.6)	2.8 (2.3)	4.9 (2.6)	3.6 (2.6)
Fatigue (0–10), mean (S.D.)	4.7 (2.7)	2.8 (2.7)	5.1 (2.7)	4.3 (2.8)
Sleep (0–10), mean (S.D.)	3.9 (3.0)	2.6 (2.7)	4.3 (2.8)	3.2 (2.9)
Physical well-being (0–10), mean (S.D.)	4.4 (2.5)	3.2 (2.3)	4.9 (2.4)	3.8 (2.5)
Emotional well-being (0–10), mean (S.D.)	3.7 (2.6)	2.8 (2.5)	4.6 (2.6)	3.4 (2.7)
Coping (0–10), mean (S.D.)	3.8 (2.5)	2.4 (2.3)	4.2 (2.6)	3.0 (2.5)
Full RAID score (0–10), mean (S.D.)	4.3 (2.2)	3.0 (2.0)	4.7 (2.3)	3.6 (2.3)

[a]Missing data for <10% of patients. [b]3v remission: TJC28, SJC28 and CRP (mg/dl) all $\leqslant 1$, but PGA not considered. It equates to merging the remission and near-remission disease states. [c]Remission: TJC28, SJC28, CRP (mg/dl) and PGA all $\leqslant 1$. [d]Near-remission: TJC28, SJC28 and CRP (mg/dl) all $\leqslant 1$ and PGA >1.

Table 2 Disease impact domains comparison according to disease activity states

Domains	Remission[a] (*n* = 195)		Near-remission[b] (*n* = 303)		Non-remission (*n* = 1090)		*P*-value	
	Mean (S.D.)	% ⩽1	Mean (S.D.)	% ⩽1	Mean (S.D.)	% ⩽1	Remission *vs* near-remission	Near-remission *vs* Non-remission
Fatigue	1.3 (1.9)	69	4.4 (2.4)	10	4.8 (2.7)	14	<0.001	0.050
Physical well-being	1.1 (1.5)	76	3.9 (2.0)	9	4.3 (2.4)	14	<0.001	0.012
Emotional well-being	1.0 (1.7)	80	3.6 (2.3)	22	3.7 (2.7)	24	<0.001	0.430
Sleep	1.0 (1.7)	80	3.5 (2.7)	28	3.6 (2.9)	31	<0.001	0.468
Pain	0.9 (1.2)	82	3.7 (2.1)	12	4.3 (2.4)	14	<0.001	<0.001
Function	0.8 (1.1)	81	3.6 (2.2)	14	4.1 (2.6)	17	<0.001	0.002
Coping	0.6 (1.2)	88	3.2 (2.3)	25	3.4 (2.5)	28	<0.001	0.324
RAID score	0.9 (1.0)	67	3.7 (1.9)	5	4.1 (2.2)	8	<0.001	0.008
PGA	0.5 (0.5)	100	3.6 (1.9)	0	4.0 (2.4)	15	<0.001	0.008

Domains in descending order by mean values in remission state. All domains are scored 0–10. *P*-values according to Student's *t*-test. [a]Remission: TJC28, SJC28, CRP (mg/dl) and PGA all ⩽1. [b]Near-remission: TJC28, SJC28 and CRP (mg/dl) all ⩽1 and PGA >1.

Drivers of PGA in near-remission patients

In the 303 near-remission patients, PGA presented moderate ($r_p = 0.47$, emotional well-being) to good ($r_p = 0.68$, pain) correlation with disease impact domains (all $P < 0.001$) (supplementary Table S2, available at *Rheumatology* Online). In multivariable analysis, PGA was explained ($R^2_{adjusted} = 0.55$) by pain ($\beta = 0.29$), function ($\beta = 0.23$), physical well-being ($\beta = 0.19$) and fatigue ($\beta = 0.15$).

Main drivers of differences of impact between disease activity states

Although both remission and near-remission patients had SJC28, TJC28 and CRP ⩽1, all mean values of impact domains were statistically higher in near-remission (supplementary Fig. S2, available at *Rheumatology* Online). Within these, physical and mixed domains of impact (pain, physical well-being, function and fatigue) presented greater ESs (~1.53) than psychological ones (still with a high ES >1.0). The same trend was found for comparisons between other disease activity groups, but with lower ESs (supplementary Fig. S2, available at *Rheumatology* Online). Global scores (PGA and RAID) were better discriminants than individual RAID domains only when comparing remission with near-remission patients (supplementary Fig. S2, available at *Rheumatology* Online).

Discussion

Several important findings emerged from this study exploring disease impact in different Boolean disease activity states. It was confirmed that ACR/EULAR Boolean-based remission is very stringent (12.3% of all patients). Near-remission, that is, failing to reach remission solely due to PGA, was at least as frequent as and up to four times more frequent than remission. Because of the influence of PGA, the percentage of patients classified as in remission was reduced from 31.4% (3v remission) to 12.3%. The scores of the diverse domains of impact in near-remission patients were similar to those for patients in non-remission and PGA was high in these patients (mean 3.6). Pain, physical well-being, function and fatigue were the impact domains that better differentiated remission from near-remission states. These results were confirmed by multivariable analyses, supporting the conclusion that high PGA in near-remission patients is driven by physical factors (which might represent subclinical inflammatory activity) and does not especially reflect psychological aspects, including anxiety or distress, or FM, contradicting common beliefs [7, 13].

This study has strengths and weaknesses. A weakness may be the relatively low percentage of patients in remission, which might limit the power. Using different multicultural cohorts imposes some cautions in the interpretation of results. However, it allowed for a larger sample and permitted us to analyse multicultural differences in PGA and its impact on the classification of remission. How PGA is measured and its relatively unclear cut-offs and formulations are another issue [7]. Using the same formulation in the three studies strengthened this pooled analysis. Some relevant comorbidities such as FM, depression and radiological damage were not assessed, although psychological distress and function were assessed through the RAID questionnaire [8]. Further studies might explore their influence on PGA. Finally, other measures of quality of life than the RAID would have strengthened this study.

One recent study explored PGA determinants in different levels of disease activity [14], but using tertiles of DAS28 instead of ACR/EULAR remission criteria [3] and the small sample rendered assessment of remission not feasible and a DAS28 <4.2 was adopted.

The ratio of near-remission *vs* remission rates was variable between studies, from 1:1 to 4:1. Possible reasons to explain this difference could include culture, which may affect PROs [15]. Other reasons could be differences in the provision of patient education, psychological support and patient expectations between countries. Near-remission rate differences could also be affected by the reliability of joint counts [16]. SJC and TJC may miss subclinical inflammation in joints [17], and totally ignore inflammation in other structures, such as tenosynovitis, which patients can still perceive and value. The use of US [18] or sensitive CRP measurement (which reflects inflammatory activity when routine CRP is $\leqslant$1) [19] rather than current methods should be further explored, especially in patients in near-remission.

As expected, patients in remission had a low disease impact. Fatigue was, among this group of patients and also among all, the domain with the highest mean score, underlining its importance in the impact of RA, even in patients in remission [20].

The findings reported herein have important implications for clinical practice. Patients in near-remission presented high levels of symptoms, with mean scores $\sim$3.5. Although a higher cut-off for PGA in the definition of remission would certainly increase the number of remissions, it would not make clinical sense in patients whose high PGA is not related to residual inflammation but to structural damage or an unrelated comorbidity such as OA, depression or FM. Such patients would require adjunctive tailored interventions (e.g. patient education, physiotherapy, analgesics, antidepressants or cognitive behavioural therapy) and not the reinforcement of disease-modifying medication recommended to those not achieving remission. Another important issue is when to stop or taper immunosuppression—is the target then remission or near-remission? The present results support the idea that PGA poses problems when used in the combined definition of remission. Perhaps having two separate definitions of remission: one for the purposes of defining the target of immunosuppressive therapy (excluding PGA) and another that is patient based would make sense.

The impact of disease from the patient's perspective should continue to be taken very seriously, but this would be better served by an instrument that allows identification of the specific cause of persistent impact and thus guide adjunctive therapy. The RAID [8], taking its individual dimensions separately, may well be a good solution to this need.

Acknowledgments

We wish to thank Dr Mwidimi Ndosi (University of the West of England, Bristol, UK) for critically revising the manuscript for its intellectual content.

The CoimbRA Investigators, in addition to authors R.J.O.F., C.D. and J.A.P.d.S. are the following: Gisela Eugénio (Coimbra, Portugal) and Cristiana Silva (Coimbra, Portugal).

The RAID Investigators, in addition to authors L.G., M.d.W., M.D., J.R.K. and T.K.K. are the following: Andra Balanescu (Bucharest, Romania), Dimitrios T. Boumpas (Heraklion, Greece), Loreto Carmona (Madrid, Spain), Ben A. C. Dijkmans (Amsterdam, The Netherlands), Matthias Englbrecht (Erlangen, Germany), Feride Gogus (Ankara, Turkey), Turid Heiberg (Oslo, Norway), Emilio Martin Mola (Madrid, Spain), Marco Matucci Cerinic (Firenze, Italy), Kati Otsa (Tallinn, Estonia), Georg Schett (Erlangen, Germany) and Tuulikki Sokka (Jyväskylä, Finland).

The COMEDRA Investigators, in addition to authors M.D., M.S., L.G. and B.F. are the following: Françoise Fayet (Clermont-Ferrand, France), Mélanie Gilson (Grenoble, France), Alain Cantagrel (Toulouse, France), Sophie Pouplin (Rouen, France), René-Marc Flipo (Lille, France), Gael Mouterde (Montpellier, France), Liana Euller-Ziegler (Nice, France), Thierry Schaeverbeke (Bordeaux, France), Alain Saraux (Brest, France), Isabelle Chary-Valckenaere (Nancy, France), Gérard Chales (Rennes, France), Emmanuelle Dernis (Le Mans, France), Pascal Richette (Paris, France), Xavier Mariette (Le Kremlin-Bicetre, France), Francis Berenbaum (Paris, France) and Jean Sibilia (Strasbourg, France).

The RAID study was supported by the EULAR (grant number CLI.013). The COMEDRA trial (NCT01315652) was supported by a grant from the French National Research Program (grant number 2010-A 01 2996-33) and an unrestricted grant from Roche.

Funding: No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article.

Disclosure statement: The authors have declared no conflicts of interest.

Supplementary data

Supplementary data are available at *Rheumatology* Online.

References

1 Smolen JS, Landewe R, Bijlsma J *et al*. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis 2017 Published Online First: 2017/03/08. doi: 10.1136/annrheumdis-2016-210715.

2 Singh JA, Saag KG, Bridges SL *et al*. 2015 American College of rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Care Res 2016;68:1–25.

3 Felson DT, Smolen JS, Wells G *et al*. American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Arthritis Rheum 2011;63:573–86.

4 Studenic P, Smolen JS, Aletaha D. Near misses of ACR/EULAR criteria for remission: effects of patient global

assessment in Boolean and index-based definitions. Ann Rheum Dis 2012;71:1702–5.

5 Vermeer M, Kuper HH, van der Bijl AE *et al*. The provisional ACR/EULAR definition of remission in RA: a comment on the patient global assessment criterion. Rheumatology 2012;51:1076–80.

6 Balogh E, Dias JM, Orr C *et al*. Comparison of remission criteria in a tumour necrosis factor inhibitor treated rheumatoid arthritis longitudinal cohort: patient global health is a confounder. Arthritis Res Ther 2013;15:R221.

7 Nikiphorou E, Radner H, Chatzidionysiou K *et al*. Patient global assessment in measuring disease activity in rheumatoid arthritis: a review of the literature. Arthritis Res Ther 2016;18:251.

8 Gossec L, Paternotte S, Aanerud GJ *et al*. Finalisation and validation of the rheumatoid arthritis impact of disease score, a patient-derived composite measure of impact of rheumatoid arthritis: a EULAR initiative. Ann Rheum Dis 2011;70:935–42.

9 Dougados M, Soubrier M, Perrodeau E *et al*. Impact of a nurse-led programme on comorbidity management and impact of a patient self-assessment of disease activity on the management of rheumatoid arthritis: results of a prospective, multicentre, randomised, controlled trial (COMEDRA). Ann Rheum Dis 2015;74:1725–33.

10 Ferreira RJO, Duarte C, Ndosi M *et al*. Suppressing inflammation in rheumatoid arthritis: Does patient global assessment blur the target? A practice–based call for a paradigm change. Arthritis Care Res 2017; doi: 10.1002/acr.23284. (in press).

11 Svensson B, Andersson ML, Bala SV, Forslind K, Hafstrom I. Long-term sustained remission in a cohort study of patients with rheumatoid arthritis: choice of remission criteria. BMJ Open 2013;3:e003554.

12 Tälli S, Etcheto A, Fautrel B *et al*. Patient global assessment in psoriatic arthritis – what does it mean? An analysis of 223 patients from the psoriatic arthritis impact of disease (PsAID) study. Joint Bone Spine 2016;83:335–40.

13 Coury F, Rossat A, Tebib A *et al*. Rheumatoid arthritis and fibromyalgia: a frequent unrelated association complicating disease management. J Rheumatol 2009;36:58–62.

14 Ward MM, Guthrie LC, Dasgupta A. Direct and indirect determinants of the patient global assessment in rheumatoid arthritis: Differences by level of disease activity. Arthritis Care Res 2017;69:323–9.

15 Putrik P, Ramiro S, Hifinger M *et al*. In wealthier countries, patients perceive worse impact of the disease although they have lower objectively assessed disease activity: results from the cross-sectional COMORA study. Ann Rheum Dis 2015;75:715–20.

16 Cheung PP, Gossec L, Mak A, March L. Reliability of joint count assessment in rheumatoid arthritis: a systematic literature review. Semin Arthritis Rheum 2014;43:721–9.

17 Saleem B, Brown AK, Keen H *et al*. Should imaging be a component of rheumatoid arthritis remission criteria? A comparison between traditional and modified composite remission scores and imaging assessments. Ann Rheum Dis 2011;70:792–8.

18 Horton SC, Tan AL, Freeston JE *et al*. Discordance between the predictors of clinical and imaging remission in patients with early rheumatoid arthritis in clinical practice: implications for the use of ultrasound within a treatment-to-target strategy. Rheumatology 2016;55:1177–87.

19 Dessein PH, Joffe BI, Stanwix AE. High sensitivity C-reactive protein as a disease activity marker in rheumatoid arthritis. J Rheumatol 2004;31:1095–7.

20 Druce KL, Bhattacharya Y, Jones GT, Macfarlane GJ, Basu N. Most patients who reach disease remission following anti-TNF therapy continue to report fatigue: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. Rheumatology 2016;55:1786–90.

SUPPLEMENTARY DATA

Supplementary Table S1. Disease impact domains in 3v-remission patients

Domains	3v-remission[a] n=498	
	Mean (SD)	% ≤1
Fatigue	3.2 (2.7)	33
Physical wellbeing	2.8 (2.3)	35
Emotional wellbeing	2.6 (2.5)	45
Sleep	2.5 (2.7)	48
Pain	2.6 (2.2)	39
Function	2.5 (2.3)	40
Coping	2.2 (2.3)	50
RAID Score	2.6 (2.1)	29
PGA	2.4 (2.2)	39

All domains are scored 0-10. Each column presents mean (SD) values and the percentage of patients that scored each domain below 1. [a]3v-remission: TJC28, SJC28, and CRP mg/dl all ≤1; PGA not considered. PGA: patient global assessment; RAID: Rheumatoid Arthritis Impact of Disease.

Supplementary Table S2. Univariable and multivariable analyses to explain Patient Global Assessment in near-remissiona patients (n=303)

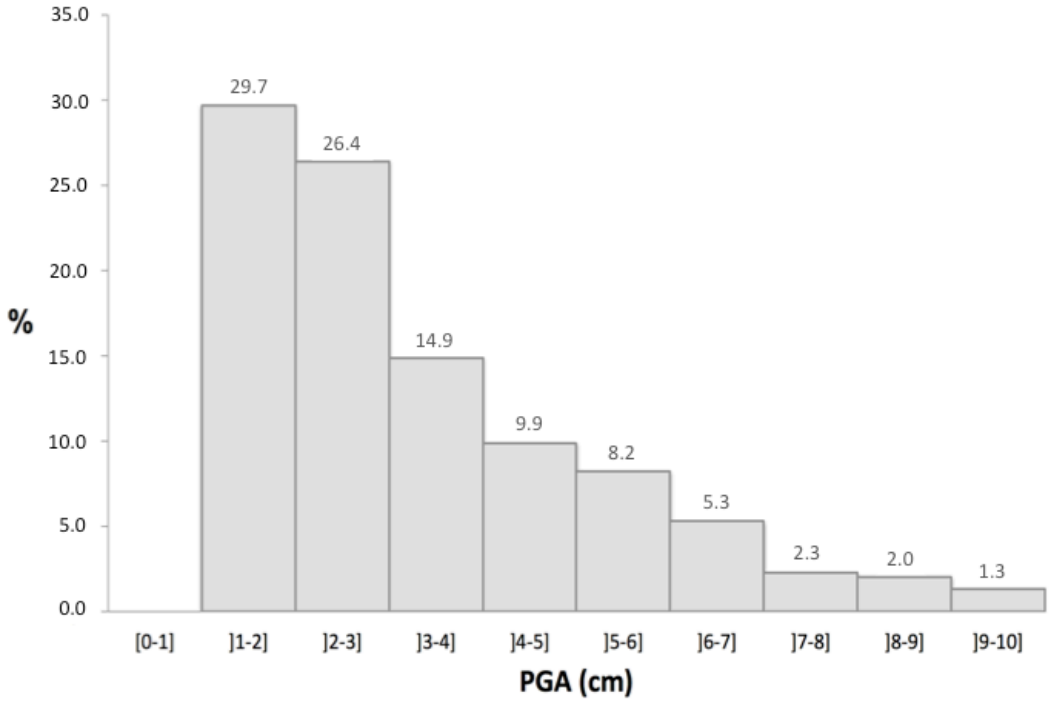
Domains	Pearson's correlation		Linear Regression[b]	
	r	p-value	$\beta_{adjusted}$	p-value
Pain	0.68	<0.001	0.29	<0.001
Function	0.67	<0.001	0.23	0.001
Physical Wellbeing	0.65	<0.001	0.19	0.006
Fatigue	0.59	<0.001	0.15	0.010
Coping	0.57	<0.001	--	--
Sleep	0.49	<0.001	--	--
Emotional Wellbeing	0.47	<0.001	--	--

Domains in descendent order of Pearson's correlation coefficient. All domains scored 0-10.

[a]Only PGA>1. PGA: patient global assessment.

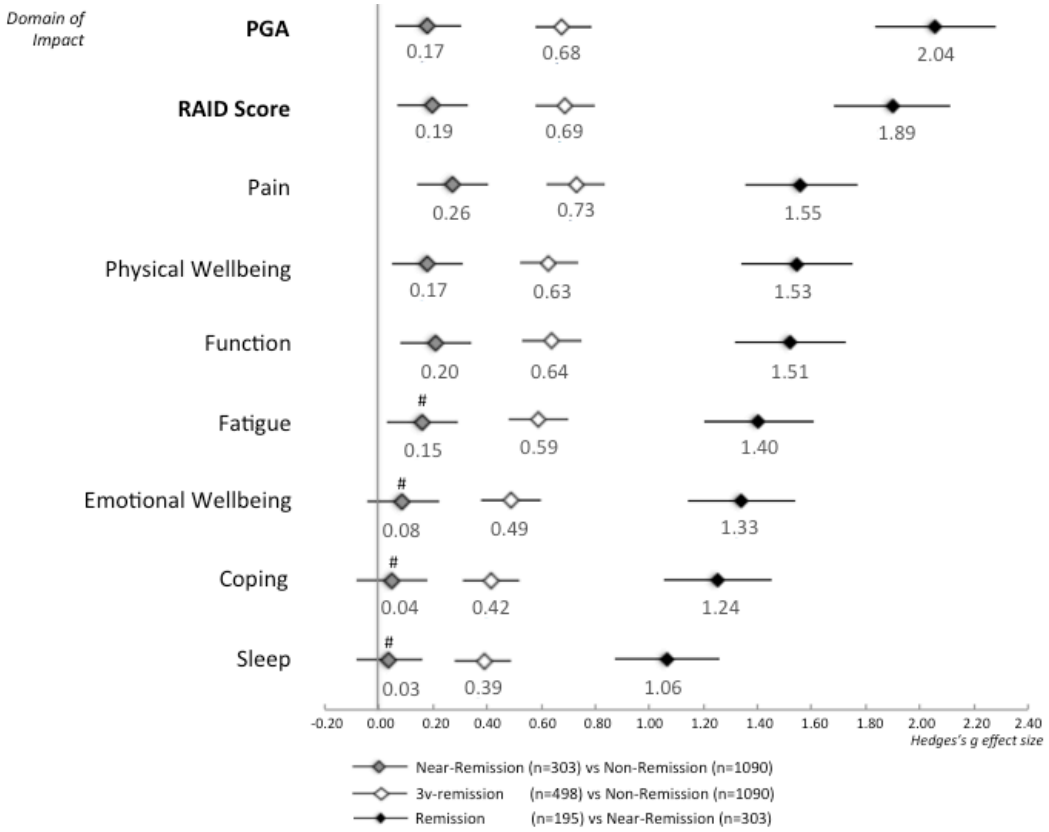
[b]$R^2_{adjusted}$=0.55.

Supplementary Figure S1. Distribution of patient global assessment in near-remission[a] patients (n=303)



[a]Only PGA>1. PGA: patient global assessment.

Supplementary Figure S2. Hedges' g effect sizes of disease impact domains to discriminate between disease activity states



Domains in descending order of black diamonds. Each diamond represents the effect size, i.e. the strength/magnitude of the mean difference between two groups (represented by different grey scales). All mean differences except the represented with a cardinal (#) were statistically significant. The horizontal bars represent the 95% confidence interval of the effect size. General guidelines to interpret effect sizes classify them as small (<0.2), medium (0.5) and large (>0.8). PGA: patient global assessment; RAID: Rheumatoid Arthritis Impact of Disease.

Manuscript 6

Impact of patient global assessment on achieving remission in patients with rheumatoid arthritis: a multinational study using the METEOR database

Ferreira RJO, Carvalho PD, Ndosi M, Duarte C, Chopra A, Murphy E, van der Heijde D, Machado PM*, da Silva JAP*

Arthritis Care Res (Hoboken). 2019 Mar 1; doi: 10.1002/acr.23866.

JOURNAL'S IMPACT FACTOR: 4.530

Number of external citations*: 1

Number of self-citations*: 0

CONFERENCES PRESENTATIONS/ABSTRACTS

Conference*:* EULAR Annual Congress 2017 (Madrid, Spain). Poster Tour.

Abstract*:* Ferreira RJO, Ndosi M, Duarte C, Carvalho P, Chopra A, Salomon-Escoto K, Vega-Morales D, van der Heijde, da Silva JAP, on behalf of METEOR investigators. SAT0718-HPR Influence of patient global assessment on the disease activity assessment in patients with rheumatoid arthritis: a meteor cross-sectional study *Ann Rheum Dis.* 76 (Suppl 2), 1510.

Journal's Impact Factor: 12.350

Number of external citations*: 0

Number of self-citations*: 1

Conference*:* XIX National Congress of the Portuguese Society of Rheumatology (Albufeira, Portugal). Oral Comunication

OTHER SCIENTIFIC OUTPUTS

Editorial: This manuscript deserved an Editorial: Pope, J. E. and Michaud, K. (2019). Is it time to banish composite measures for remission in RA? Arthritis Care Res. doi:10.1002/acr.23862

Research Grant: A competitive research grant awarded (8,305.00€) by MERIT foundation in 2016 (Ferreira RJO first author)

* until 30th august 2019

Arthritis Care & Research
Vol. 0, No. 0, Month 2019, pp 1–9
DOI 10.1002/acr.23866

American College of Rheumatology
Empowering Rheumatology Professionals

Impact of Patient's Global Assessment on Achieving Remission in Patients With Rheumatoid Arthritis: A Multinational Study Using the METEOR Database

Ricardo J. O. Ferreira,[1] Pedro David Carvalho,[2] Mwidimi Ndosi,[3] Cátia Duarte,[4] Arvind Chopra,[5] Elizabeth Murphy,[6] Désirée van der Heijde,[7] Pedro M. Machado,[8] and José A. P. da Silva[4]

Objective. There is an ongoing debate about excluding patient's global assessment (PtGA) from composite and Boolean-based definitions of rheumatoid arthritis (RA) remission. This study aimed at determining the influence of PtGA on RA disease states, exploring differences across countries, and understanding the association between PtGA, measures of disease impact (symptoms), and markers of disease activity (inflammation).

Methods. Cross-sectional data from the Measurement of Efficacy of Treatment in the Era of Outcome in Rheumatology international database were used. We calculated the proportion of patients failing American College of Rheumatology/European League Against Rheumatism Boolean-based remission (4-variable remission) solely due to PtGA (PtGA-near-remission) in the overall sample and in the most representative countries (i.e., those with >3,000 patients in the database). Multivariable linear regression models were used to identify the main determinants of PtGA, grouped in predominantly inflammatory impact factors (28 tender joint counts, 28 swollen joint counts, and C-reactive protein level) and disease impact factors (pain and function).

Results. This study included 27,768 patients. Excluding PtGA from the Boolean-based definition (3-variable remission) increased the remission rate from 5.8% to 15.8%. The rate of PtGA-near-remission varied considerably between countries, from 1.7% in India to 17.9% in Portugal. One-third of the patients in PtGA-near-remission group scored PtGA >4 of 10. Pain and function were the main correlates of PtGA, with inflammation-related variables contributing less to the model (R^2 = 0.57).

Conclusion. PtGA is moderately related to joint inflammation overall, but only weakly so in low levels of disease activity. A considerable proportion of patients otherwise in biologic remission still perceive high PtGA, putting them at risk of excessive immunosuppressive treatment.

INTRODUCTION

Remission is now the target of treatment in rheumatoid arthritis (RA) (1,2). However, the percentage of patients achieving remission is strongly influenced by the remission definition used (3), and there is currently no consensus on which definition is the most appropriate to support a treat-to-target approach (4). The most authoritative definition, adopted jointly by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) (5), provides 2 alternative definitions: either a Boolean-based definition (28 swollen joint count [SJC28], 28 tender joint count [TJC28], C-reactive protein [CRP; mg/dl] level, and patient's global assessment [PtGA; 0–10-cm scale], all ≤1), or a Simplified Disease Activity Index (SDAI) ≤3.3. The SDAI is calculated from the simple sum of the 4 Boolean components and the physician global assessment (0–10-cm scale). Two other commonly used

The views expressed are those of the authors and not necessarily those of the National Health Service, the NIHR, or the UK Department of Health.

Mr. Ferreira's work was supported by the Merit Foundation (RP 2015-01). Dr. Machado's work was supported by the NIHR, University College London Hospitals, and the Biomedical Research Centre.

[1]Ricardo J. O. Ferreira, RN, MSc: Centro Hospitalar e Universitário de Coimbra, and Health Sciences Research Unit: Nursing, Nursing School of Coimbra, Coimbra, Portugal; [2]Pedro David Carvalho, MD: Centro Hospitalar e Universitário do Algarve, Algarve Biomedical Center, Faro, and Lisbon Academic Medical Center, Lisbon, Portugal; [3]Mwidimi Ndosi, RN, PhD: University of the West of England, Bristol, UK; [4]Cátia Duarte, MD, José A. P. da Silva, MD, PhD: Centro Hospitalar e Universitário de Coimbra, Coimbra Institute for Clinical and Biomedical Research, and University of Coimbra, Coimbra, Portugal; [5]Arvind Chopra, MD, PhD: Centre for Rheumatic Diseases, Pune, India; [6]Elizabeth Murphy, MD: University Hospital Wishaw, Wishaw, Scotland; [7]Désirée van der Heijde, MD, PhD: Leiden University Medical Centre, Leiden, The Netherlands; [8]Pedro M. Machado, MD, PhD: University College London, University College London Hospitals NHS Foundation Trust, and London North West University Healthcare NHS Trust, London, UK.

No potential conflicts of interest relevant to this article were reported.

Drs. Machado and da Silva contributed equally to this work.

Address correspondence to Ricardo J. O. Ferreira, RN, MSc, Serviço de Reumatologia, Centro Hospitalar Universitário de Coimbra, EPE. 3000-075 Coimbra, Portugal. E-mail: rferreira@reumahuc.org.

Submitted for publication August 11, 2018; accepted in revised form February 26, 2019.

SIGNIFICANCE & INNOVATIONS

- Among 27,768 patients with rheumatoid arthritis from a large number of countries, 10% failed to reach American College of Rheumatology/European League Against Rheumatism Boolean-based remission only due to a patient's global assessment (PtGA) >1, and among these, approximately 1 of 3 scored the PtGA >4 (0–10 scale).
- PtGA showed a moderate-to-poor relationship with disease activity, especially at levels close to defined treatment targets.
- The inclusion of PtGA in definitions of remission may lead to overtreatment with immunosuppressive drugs.
- The patient's perspective remains essential to patient care. However, a separation between inflammatory and disease impact targets will probably improve safety and outcomes from the patients' perspective.

definitions are based on the 28-joint count Disease Activity Score (DAS28), either with 4 or 3 variables (i.e., with or without PtGA), (6) or the Clinical Disease Activity Index (CDAI; with the same formula as the SDAI, but without the CRP level) (7,8).

PtGA is included in all these definitions, except in the 3-variable DAS28, but there is an ongoing debate regarding whether the PtGA should remain in the definition. Its inclusion has been justified because PtGA tends to accompany disease activity (inflammation control) in clinical trials of RA (5) and because it conveys the patient perspective, which is obviously core to the objectives of treatment (9). However, a growing concern has emerged as to whether PtGA reflects disease activity at the biologic inflammatory process close enough to make it an appropriate instrument to define the target for immunosuppressive therapies (10–12), namely in long-term follow-up and in low–disease activity populations followed in clinical practice. Support for this idea has been demonstrated by a low correlation of PtGA with joint counts and acute-phase reactants (10,13,14), and by PtGA being unrelated to structural damage or other important outcomes (15,16) that treat-to-target aims to prevent. PtGA is highly affected by comorbidities and by other musculoskeletal and psychological conditions (e.g., osteoarthritis, fibromyalgia, depression) that cannot be improved by therapies targeting the inflammatory process, which makes it inappropriate to guide the readjustment of such therapies (11,17,18). Additionally, concerns have been raised regarding the variety of formulations used to ask this question (18), which have been shown to influence remission rates by 4.7% to 6.3% (19). The patient's health literacy also affects the validity and reliability of PtGA: approximately 40% of patients find the concept of PtGA confusing and the instruments difficult to mark (20).

The importance of understanding how PtGA influences disease activity classification became especially important with the new ACR/EULAR remission criteria, given that a PtGA score >1 excludes remission, even if all the other 3 criteria are ≤1 (a condition referred to as PtGA-near-remission state). Several independent studies have shown that 14% to 38% of patients with RA, in different settings, are in PtGA-near-remission (10,21–25), although these proportions need to be confirmed in larger international samples. The main issue is that following current treatment recommendations (1,2), this state of PtGA-near-remission would justify intensification of immunosuppressive treatment, after considering "other patient factors, such as progression of structural damage, comorbidities, and safety issues" (1), or the "patient's individual circumstances" (2). Treatment decisions have been regarded as more nuanced and most rheumatologists would be unlikely to base a treatment escalation decision on the value of the PtGA alone (26). The question remains: if it is acceptable that rheumatologists ignore PtGA for treatment decisions, then why should it be kept in target definitions? Other researchers have proposed the increase of the cutoff point of PtGA to approximately 2.5 or 3 cm (27,28), but this suggestion does not solve the problems of validity and reliability mentioned above.

Members of our group (10,29) have proposed the dual-target concept, involving concomitant and obligatory use of 2 different targets: a measure of inflammatory disease activity (biologic remission or 3-variable remission) and a measure of patient-reported impact of the disease (symptom remission). The latter should be based on patient-reported outcomes (PROs) that are better than PtGA at discriminating disease impact and thus help to guide adjunctive therapy (10,29). This proposal has ignited controversy (12,26). The concepts being addressed are of crucial importance in defining management strategies, supporting the need for further studies to enlighten the ongoing debate (30). Measurement of Efficacy of Treatment in the Era of Outcome in Rheumatology (METEOR), a large international longitudinal database, reflecting current clinical practice, provides a valuable opportunity to take into account the variability of clinical settings of care provision, including differences in cultural background, as well as treatment accessibility and standards.

The objectives of the current study were to determine the influence of PtGA on the classification of patients according to disease activity states, particularly remission, and explore differences across countries, to explore the range of PtGA values among patients in remission by DAS28 and in PtGA-near-remission, and to determine the associations of PtGA with markers of inflammation and of impact of disease.

PATIENTS AND METHODS

Patients and study design. This study used data from the METEOR database, an ongoing prospective international register of patients with RA founded in 2006 (31,32). The METEOR is a free web-based tool available worldwide, containing >45,000 patients,

>33 countries, and >270,000 visits, corresponding to a mean ± SD of 3.1 ± 3.1 person-years of follow-up. Data regarding patients' sociodemographics, diagnosis, treatment, and follow-up, according to usual care, are collected anonymously in a central database. Data can also be uploaded from local electronic health record systems or registries, which is the case in The Netherlands, Portugal, India, and other countries (31,32). All data in METEOR are fully anonymized and all follow-up visits, measurements, and medication are based on daily clinical practice; therefore, medical ethics approval is not required. For this study, the first visits of patients registered in METEOR, from adult patients with no missing data in the variables used to determine ACR/EULAR Boolean-based remission status, were selected. The database included visits from June 1985 until December 2017.

Assessments. PtGA of the current disease activity was measured on a 0–10-cm visual analog scale (VAS), with anchors of 0 (not active at all) and 10 (extremely active). Although the meaning of the question was the same, the exact formulation of the question varied across countries. Other PROs assessed were pain (VAS, 0–10 cm) and physical function, measured by the Health Assessment Questionnaire disability index (HAQ DI) (33). The following clinical and demographic parameters were also considered for sample characterization: sex, age at visit, disease duration since diagnosis, gross domestic product per capita of the country, the presence of erosions, and current treatment with biologic disease-modifying antirheumatic drugs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs).

Definitions of remission. The ACR/EULAR Boolean-based definition (5) was adapted to classify patients in 3 main remission states: Boolean-based remission (TJC28, SJC28, CRP level mg/dl, and PtGA, all ≤1), also designated in this study as 4-variable remission; PtGA-near-remission (TJC28, SJC28, CRP level mg/dl, all ≤1, and only PtGA >1) (10); and nonremission (if 2 or more criteria are >1). The proposed binary definition of 3-variable remission (the same criteria as 4-variable remission but excluding PtGA) (10,16) was also tested. Naturally, 3-variable remission is equal to 4-variable remission + 4-variable PtGA-near-remission. The proportions of patients who failed Boolean remission due to a single criterion, other than PtGA, were also calculated (21).

An even stricter 3-variable Boolean-based criterion, defined by the authors as SJC28 = 0, TJC28 = 0, and CRP level (mg/dl) ≤0.5 (strict 3-variable remission) was used in exploratory analyses to assess the percentage of patients scoring PtGA ≤1 under these circumstances. The remission definitions of SDAI (≤3.3) and CDAI (≤2.8) (7,8) were also used to establish their prevalence among patients in the PtGA-near-remission state. For DAS28, remission states were assessed with the DAS28-CRP (34) because it was available in more patients than DAS28-ESR, and because the other definitions of remission also include the CRP level. We used the most recently proposed cutoffs (35).

Statistical analysis. Data were analyzed using SPSS Statistics software, version 20.0. Quantitative data were expressed as means ± SDs and categorical data as frequencies and percentages. The influence of PtGA in the rates of remission according to the various definitions was assessed in 2 ways: by comparing the remission rates according to 4-variable DAS28-CRP versus 3-variable DAS28-CRP, and by determining the proportion of patients in PtGA-near-remission (Boolean definition). Secondary analyses included determining the distribution of PtGA values from patients fulfilling DAS28-CRP remission, PtGA-near-remission, and strict 3-variable remission, and determining the proportion of patients in PtGA-near-remission who were also in SDAI and CDAI remission states.

Pearson's correlation coefficients between PtGA, and SJC28, TJC28, CRP level, 3-variable DAS28-CRP, pain scores, and function (HAQ DI) were calculated and categorized as high (r ≥ 0.60), moderate (r = 0.40–0.59), and low (r < 0.40) (36). Correlations with 3-variable DAS28-CRP were separately

Table 1. Summary of the clinical and demographic characteristics of the study population (n = 27,768)*

Variable	Observed values	Missing %
Female, no. (%)	21,976 (79.7)	0.7
Age at visit, years	52.6 ± 14.1	1.8
National GDP >20,000, %†	16,319 (59.7)	1.5
Disease duration since diagnosis, years‡	4.3 ± 7.3	7.6
Year of diagnosis 2000 or later, no. (%)	21,430 (83.4)	7.6
Rheumatoid factor positive, no. (%)	17,076 (74.7)	17.7
ACPA positive, no. (%)	11,533 (71.5)	58.1
Erosions, no. (%)	7,359 (54.6)	51.4
Treatment with steroids, no. (%)	10,407 (37.5)	0.0
Treatment with csDMARDs, no. (%)	19,556 (70.4)	0.0
Treatment with bDMARDs, no. (%)	6,449 (23.2)	0.0
Treatment with tsDMARDs, no. (%)	2 (<0.1)	0.0
TJC28	9.1 ± 9.0	0.0
SJC28	4.6 ± 5.3	0.0
CRP mg/dl	2.2 ± 3.0	0.0
PtGA (0–10 scale)	4.9 ± 2.6	0.0
3-variable DAS28-CRP	4.2 ± 2.6	0.0
SDAI remission (≤3.3), no. (%)	1,419 (6.4)	20.8
CDAI remission (≤2.8), no. (%)	1,418 (6.4)	20.8
Pain (VAS 0–10 scale)	4.9 ± 2.6	9.3
HAQ DI (0–3 scale)	1.1 ± 0.7	20.0

* Values are the mean ± SD unless indicated otherwise. One visit only per patient (the first visit providing all Boolean criteria). GDP = gross domestic product; ACPA = anti-citrullinated protein antibody; csDMARDs = conventional synthetic disease-modifying antirheumatic drugs; bDMARDs = biologic DMARDs; tsDMARDs = target synthetic DMARDs; TJC28 = 28 tender joint count; SJC28 = 28 swollen joint count; CRP = C-reactive protein; PtGA = patient's global assessment; DAS28-CRP = Disease Activity Score with 28-joint counts using CRP level; SDAI = Simplified Disease Activity Index; CDAI = Clinical Disease Activity Index; VAS = visual analog scale; HAQ DI = Health Assessment Questionnaire disability index.
† International dollars.
‡ This definition was chosen instead of time since the date of the onset of symptoms because the latter had significantly more missing data (28.2%; mean ± SD 6.9 ± 8.1 years).

Table 2. Impact of patient's global assessment (PtGA) in the various remission criteria, in the overall sample and by country*

Disease activity status	Overall (n = 27,768)	Netherlands (n = 3,296)	Italy (n = 4,156)	Portugal (n = 4,373)	India (n = 8,936)	Other (n = 7,007)
ACR/EULAR Boolean-based						
4-variable remission†	1,605 (5.8)	202 (6.1)	243 (5.8)	395 (9.0)	5 (0.1)	760 (10.8)
PtGA-near-remission‡	2,776 (10.0)	453 (13.7)	293 (7.1)	784 (17.9)	151 (1.7)	1,095 (15.6)
Nonremission§	23,387 (84.2)	2,641 (80.2)	3,620 (87.1)	3,194 (73.1)	8,780 (98.2)	5,152 (73.6)
Proposed 3-variable remission¶	4,381 (15.8)	655 (19.8)	536 (12.9)	1,179 (26.9)	156 (1.8)	1,855 (26.4)
Near-remission only#						
Due to PtGA	2,776 (79.7)	453 (74.1)	293 (78.3)	784 (82.4)	151 (91.5)	1,095 (79.4)
Due to CRP	271 (7.8)	57 (9.3)	31 (8.3)	82 (8.6)	5 (3.0)	96 (7.0)
Due to TJC28	249 (7.2)	63 (10.3)	32 (8.6)	47 (4.9)	8 (4.8)	99 (7.2)
Due to SJC28	185 (5.3)	38 (6.2)	18 (4.8)	39 (4.1)	1 (0.6)	89 (6.5)
3-variable DAS28-CRP**						
Remission (<2.4)	4,629 (16.7)	601 (18.2)	561 (13.5)	1,269 (29.0)	142 (1.6)	2,056 (29.3)
Low (≥2.4 to ≤2.9)	2,258 (8.1)	434 (13.2)	313 (7.5)	514 (11.8)	210 (2.4)	787 (11.3)
4-variable DAS28-CRP**						
Remission (<2.4)	4,131 (14.9)	551 (16.7)	503 (12.1)	1,130 (25.8)	96 (1.1)	1,851 (26.4)
Low (≥2.4 to ≤2.9)	1,957 (7.0)	395 (12.0)	236 (5.7)	468 (10.7)	150 (1.7)	708 (10.1)
Differences between 3-variable and 4-variable definitions, %						
DAS28-CRP remission/low	1.8/2.9	1.5/2.7	1.4/3.2	3.2/4.3	0.5/1.2	2.9/4.1
ACR/EULAR Boolean remission	10.0	13.7	7.1	17.9	1.7	15.6

* Values are the number (%) unless indicated otherwise. ACR = America College of Rheumatology; EULAR = European League Against Rheumatism; CRP = C-reactive protein; TJC28 = 28 tender joint count; SJC28 = 28 swollen joint count; DAS28-CRP = Disease Activity Score with 28-joint counts using CRP level.
† 4-variable remission = TJC28, SJC28, CRP level mg/dl, and PtGA, all ≤1.
‡ PtGA-near-remission = TJC28, SJC28, and CRP level mg/dl, all ≤1, with PtGA >1.
§ Nonremission = 2 or more of the 4 criteria (TJC28, SJC28, CRP level, or PtGA) >1.
¶ TJC28, SJC28, and CRP level mg/dl all ≤1; PtGA not considered. This proposed remission definition equates to merging 4-variable remission and "PtGA-near-remission" disease states.
# Near-remission = only 1 of the 4 criteria (TJC28, SJC28, CRP level, or PtGA) >1.
** The cutoffs proposed by Fleischmann et al (35) were used.

assessed for patients in remission/low disease activity, because this is the subgroup where the use of PtGA in managing treatment according to current recommendations has the greatest impact. Differences between the most represented countries (n >3,000 patients) in the database were explored. Multivariable linear regression models (using the Enter method, with all variables) with PtGA as a dependent variable were used to analyze the main determinants of the PtGA from 2 primary domains: predominantly inflammatory (SJC28, TJC28, CRP level) and patient-reported impact measures (pain and function).

RESULTS

Patient characteristics. Among the 43,341 patients (264,920 visits) available in the database, only 27,768 patients/visits were included (i.e., the first among 109,556 recorded visits without missing data in the 4 Boolean criteria). Table 1 shows the patient characteristics, representing 32 countries (also see Supplementary Table 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23866/abstract). Mean ± SD disease duration since diagnosis was 4.3 ± 7.3 years, 83.4% of patients were diagnosed from the year 2000 onward, and 23.2% of the patients were currently receiving bDMARDS. The mean ± SD 3-variable DAS28-CRP was 4.2 ± 2.6 and the mean ± SD PtGA was 4.9 ± 2.6.

Influence of PtGA in remission states. The overall remission rate according to the ACR/EULAR Boolean-based definition was 5.8%. An additional 10.0% of patients failed to achieve remission solely because of PtGA (PtGA-near-remission patients). The rate of PtGA-near-remission across countries was 1.7% in India, 7.1% in Italy, 13.7% in The Netherlands, 15.6% in other countries, and 17.9% in Portugal (Table 2).

Altogether, the remission rate would increase from 5.8% to 15.8% if the Boolean 3-variable remission was used instead of the 4-variable, i.e., if PtGA was excluded from the definition. The maximum difference was observed in Portugal: from 9.0% to 26.9% (Table 2). PtGA was clearly the major obstacle to 4-variable remission, justifying 79.7% of all the cases of near-remission in the overall sample.

The inclusion of PtGA in the DAS28-CRP formula led to a drop of 1.8% in the remission rate in the overall sample (16.7% versus 14.9%) (Table 2), a difference that varied from 0.5% in India to 3.2% in Portugal. If the low disease activity state was considered the target, the decrease in rate imposed by PtGA was 2.9% in the overall sample (24.8% versus 21.9%), reaching a maximum difference of 4.3% in Portugal.

PtGA values among patients in near-remission and strict 3-variable remission. Figure 1 shows the distribution of PtGA in these patients with low or null signs of inflamma-

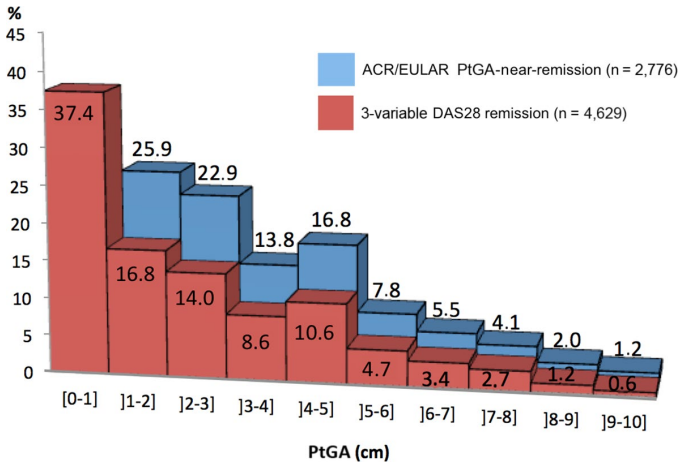


Figure 1. Patient's global assessment (PtGA) distribution in patients with rheumatoid arthritis in remission by the Disease Activity Score with 28-joint counts using the C-reactive protein and 3 variables (DAS28-CRP) and in PtGA-near-remission. PtGA-near-remission patients are defined as having 28 tender joint counts ≤1, 28 swollen joint counts ≤1, CRP level (mg/dl) ≤1, and PtGA >1 of 10. In the blue graph there are no patients within the 0–1 interval (those patients were classified as being in American College of Rheumatology [ACR]/European League Against Rheumatism [EULAR] Boolean-based remission).

tion, showing that a considerable proportion report a high PtGA: 37.4% of patients in ACR/EULAR Boolean PtGA-near-remission had a PtGA >4 of 10. The mean ± SD PtGA in these patients was 3.9 ± 2.0 for the overall sample, with similar values in the different countries (Table 3). Among patients in PtGA-near-remission, 13.1% and 9.8% were in SDAI and CDAI remission states, respectively (data not shown).

Considering only the patients with SJC28 = 0, TCJ28 = 0, and CRP level mg/dl ≤0.5, defined here as strict 3-variable remission (n = 2,395), only 43.5% had a PtGA ≤1, and 20.0% had a PtGA >4. The mean ± SD PtGA among patients in 3-variable DAS28-CRP remission was 2.5 ± 2.3 cm, while for patients in a low disease activity state, it was 3.7 ± 2.4 cm (Table 3).

PtGA associations with inflammation-related variables and with disease impact measures. In the overall sample, the correlation of PtGA was strong with pain (r_p = 0.75), moderate with function (r_p = 0.52), and 3-variable DAS28-CRP (r_p = 0.51), and weak with the individual components of 3-variable DAS28-CRP (all $P < 0.001$) (Table 4). The correlation between 3-variable DAS28-CRP and PtGA in patients in remission and in low disease activity was 0.25. These correlations varied considerably across countries, with patients from The Netherlands and India presenting the lowest correlations between PtGA and inflammatory and patient-reported measures. There was a clear relationship between DAS28 and PtGA: the mean value of PtGA in patients with high disease activity, as defined by DAS28, was 6.2 as compared to 2.5 for patients in remission (Table 3). In

Table 3. Mean values of patient's global assessment (PtGA) across disease activity states*

Disease activity status	Overall (n = 27,768)	Netherlands (n = 3,296)	Italy (n = 4,156)	Portugal (n = 4,373)	India (n = 8,936)	Other countries (n = 7,007)
ACR/EULAR Boolean-based PtGA near remission						
Remission†	0.4 ± 0.4	0.4 ± 0.4	0.3 ± 0.4	0.4 ± 0.4	0.0 ± 0.0	0.4 ± 0.4
PtGA-near-remission‡	3.9 ± 2.0	3.8 ± 1.9	4.2 ± 2.2	3.9 ± 1.9	3.8 ± 1.6	3.8 ± 2.0
Nonremission§	5.3 ± 2.4	4.1 ± 2.6	6.1 ± 2.5	5.1 ± 2.6	5.5 ± 1.8	5.2 ± 2.7
3-variable DAS28-CRP¶						
Remission (<2.4)	2.5 ± 2.3	2.6 ± 2.2	2.4 ± 2.4	2.7 ± 2.3	3.7 ± 1.6	2.4 ± 2.3
Low (≤2.9)	3.7 ± 2.4	3.2 ± 2.3	4.0 ± 2.6	3.6 ± 2.4	4.2 ± 1.8	3.7 ± 2.5
Moderate (≤4.6)	4.9 ± 2.3	4.0 ± 2.5	4.0 ± 2.5	4.9 ± 2.4	4.9 ± 1.8	4.9 ± 2.4
High (>4.6)	6.2 ± 2.1	4.8 ± 2.6	7.2 ± 2.1	6.5 ± 2.2	5.9 ± 1.7	6.8 ± 2.2

* Values are the mean ± SD in cm. ACR = American College of Rheumatology; EULAR = European League Against Rheumatism; DAS28-CRP = Disease Activity Score with 28-joint counts using C-reactive protein level and 3 variables.
† Remission = 28 tender joint count (TJC28), 28 swollen joint count (SJC28), CRP level mg/dl, and PtGA, all ≤1.
‡ PtGA-near-remission = TJC28, SJC28, CRP level mg/dl, all ≤1, and PtGA >1.
§ Nonremission = TJC28 or SJC28 or CRP level mg/dl >1, irrespective of PtGA value.
¶ The cutoffs proposed by Fleischmann et al (35) were used.

Table 4. Pearson's coefficient correlations between patient's global assessment (PtGA) and inflammatory and disease impact measures by country and by disease activity status*

Country	TJC28	SJC28	CRP mg/dl	3-variable DAS28-CRP	Pain (0–10)†	HAQ DI‡
All countries (n = 27,768)	0.43	0.36	0.23	0.51	0.75	0.52
Netherlands (n = 3,296)	0.27	0.17	0.13	0.30	0.57	0.39
Italy (n = 4,156)	0.51†	0.42	0.18	0.58	0.86	0.57
Portugal (n = 4,373)	0.48	0.40	0.21	0.54	0.86	0.57
India (n = 8,936)	0.30	0.20	0.20	0.34	0.65	0.50
Other countries (n = 7,007)	0.52†	0.43	0.24	0.59	0.74	0.56

* Values are the PtGA correlation. $P < 0.001$ in all instances. TJC28 = 28 tender joint count; SJC28 = 28 swollen joint count; CRP = C-reactive protein; DAS28-CRP = Disease Activity Score with 28-joint counts using CRP level and 3 variables; HAQ DI = Health Assessment Questionnaire disability index.
† Percentage of missing data for pain on a VAS scale was 9.3% (overall), 18.6% (Netherlands), 4.3% (Italy), 21.4% (Portugal), <0.1% (India), and 12.1% (other).
‡ Percentage of missing data for HAQ DI was 19.9% (overall), 49.0% (Netherlands), 13.8% (Italy), 21.6% (Portugal), 6.9% (India), and 25.5% (other).

multivariable analysis, pain ($\beta_{standardized}$ = 0.591) and function ($\beta_{standardized}$ = 0.156) were the main explanatory factors of PtGA. To a smaller extent, TJC28 ($\beta_{standardized}$ = 0.111), CRP level ($\beta_{standardized}$ = 0.034), and SJC28 ($\beta_{standardized}$ = 0.030) were also statistically significant in the model, which explains 57.3% of PtGA variance ($P < 0.001$) (Table 5).

DISCUSSION

This study assessed the influence of PtGA on the classification of patients' remission status according to 2 definitions, using a large international clinical practice cohort, and tested its associations with factors predominantly associated with inflammatory activity or with the impact of disease. Overall, the ACR/EULAR Boolean-based (4-variable) remission was achieved by 5.8% of the patients, but another 10% failed to meet criteria for this status solely because of PtGA >1. This difference varies across countries, from 1.7% in India to 17.9% in Portugal. Previous studies (10,21–25) have reported PtGA-near-remission rates between 14% (n = 236 European patients) (25) and 38% (n = 309 patients from Coimbra, Portugal) (10). Obviously, dropping a factor from an equation, especially if Boolean, will lead to an increase in the proportion of observations being determined/filtered. However, PtGA stands out from the other factors used to define remission because it is much more subjective than other factors and conveys information that is unrelated to inflammation, it cannot be expected to improve with immunosuppressive therapy in patients who are otherwise in remission, and it is responsible for 10-fold more cases of near-remission in the Boolean-based definition than each of the others factors (10.0% versus 1.0%, 0.9%, and 0.7% for CRP level, TJC28, and SJC28, respectively) (Table 2).

These results demonstrate a remarkable impact of PtGA on the rate of patients achieving treatment target and suggest that 10% of RA patients overall and up to 38% of all RA patients in certain settings (10) may be exposed to an overtreatment risk, if rheumatologists adhere strictly to the current Boolean definition of target (29). This possibility is certainly worrying, unless PtGA is shown to represent disease dimensions that are amenable to improvement by the therapies being considered, typically immunosuppressive agents, but this possibility is not supported by our data.

If we consider only the patients whose treatment is recommended to increase based solely on PtGA (PtGA-near-remission), PtGA shows no relationship with disease activity (Table 5), nor should it be expected to, given that SJC28, TJC28, and CRP level (mg/dl) are all ≤1. The observation that 20% of the 2,395 patients in strict 3-variable remission scored PtGA >4 underlines this interpretation and questions the possibility that high PtGA values in such patients may be a reflection of subclinical inflammation (37,38). Although PtGA has been previously

Table 5. Multivariable linear regression analysis to explain patient's global assessment (n = 20,719)*

Variable	Unstandardized β	β	*P*†	95% CI for β	Adjusted R^2	*P*
Constant	1.232	–	<0.001	1.181–1.284	0.573	<0.001
TJC28	0.030	0.111	<0.001	0.027–0.033	–	–
SJC28	0.014	0.030	<0.001	0.009–0.19	–	–
CRP mg/dl	0.027	0.034	<0.001	0.019–0.035	–	–
Pain	0.058	0.591	<0.001	0.057–0.059	–	–
HAQ DI	0.548	0.156	<0.001	0.510–0.585	–	–

* Using Enter's method and 28 tender joint count (TJC28), 28 swollen joint count (SJC28), C-reactive protein (CRP) level, pain, and Health Assessment Questionnaire disability index (HAQ DI) as independent variables. 95% CI = 95% confidence interval.

attributed high face validity in overall samples of RA patients (18), PtGA's validity becomes obviously questionable in patients with low or absent signs of active inflammation. Confounding factors, namely the different interpretation of nonstandardized questions (20,39), and the impact of unrelated factors, such as comorbidities or psychological distress, become of paramount importance (10,18,40).

Our data also demonstrate, as expected, that PtGA has a positive correlation with disease activity. Considering the overall sample, PtGA was associated with pain and function (HAQ DI) and also, although to a lesser extent, with objective measures of disease activity (SJC28, CRP level). Explaining the discrepancy observed between countries regarding the correlation between PtGA and parameters of disease activity is beyond the scope of this article. A multitude of factors, including patient education on PROs and patient expectations, are probably involved (39,41,42).

Overall, mean values of PtGA were lower in patient's groups with lower indices of disease activity, which is true at the group level (40). However, if we adopt the treat-to-target strategy, classification becomes individual and dichotomized (remission versus non-remission), and correlations are no longer relevant, because even factors with a good correlation may become inadequate for classification. This concept is critical in situations when classification has important treatment implications.

The current study has some strengths and limitations**.** METEOR also incorporates data imported from other registries and the formulation of the PtGA question presented to patients is not exactly the same. Our previous research (19) suggests that PtGA score varies by different formulations of the question. There was a significant amount of missing data (e.g., body mass index, smoking status, erosions) that could introduce some selection bias. A sizeable proportion of the PtGA variance was not explained by our models, in part because other variables that have been shown to impact PtGA, such as fatigue and stiffness, are not available in METEOR. Because health-related quality of life measures are not included in the METEOR, we were unable to assess the correlation between PtGA and quality of life. However, other studies have demonstrated that PtGA correlates better with quality-of-life measures than with these predominantly inflammatory measures (43). There may also exist a selection bias derived from the fact that countries/centers that adopt a more regular metrology, and thus contribute to cooperative databases, are the ones with better adherence to therapeutic guidelines. In our analyses, we have compared results across countries with quite different levels of income and cultural background. As main strengths of this study, we used a large database, from clinical practice and from rich and poor countries, with a diversity of cultural backgrounds. In addition, we used both simple and powerful statistical analyses, allowing easier interpretation and implementation of the results in clinical practice, while providing strong evidence for practice and further research.

Taken together, the current results and published evidence suggest that PtGA has a general correlation with disease activity level, which makes it an appropriate component of indices used for a semiquantitative evaluation of disease status, in a strategy aimed at making the patient better. This information also demonstrates, however, that PtGA lacks specificity and biologic support around the cutoff points used to define treatment target and make therapeutic decisions, as demonstrated by a correlation of just 0.25 with 3-variable DAS28-CRP in patients in low disease activity and remission states. A target should, by definition, be sharp and meaningful, especially when we are dealing with targeted immunosuppressive agents. The mean value of PtGA for patients otherwise in remission (3.9 cm) and its distribution (37% with a PtGA >4) suggest that this lack of specificity of PtGA cannot be properly resolved by simply increasing its maximum acceptable value to 2 or 3, as previously suggested (27,28).

The evidence supports our proposal for a dual-target strategy to manage RA (10,29): a biologic remission target, aiming at the control of inflammation, defined by the 3-variable remission concept and used to guide immunosuppressive therapy, and a symptom-remission target, defined by a well-validated and discriminative PRO, such as the Rheumatoid Arthritis Impact of Disease score, to guide adjuvant therapy for the control of the disease impact factors (symptom remission). Achieving inflammatory remission should be seen as a strong contribution toward remission of disease impact, but not as a guarantee. Both targets should be considered independent but obligatory and complementary, requiring equal attention from rheumatologists and the care team (12). The full resolution of the impact of disease on patients' lives (the ultimate objective of treatment) will certainly require a multidisciplinary approach involving nurses, physiotherapists, occupational therapists, psychologists, and other health care professionals. This dual target strategy and separation of measures would ensure that remission is more meaningful to patients, while such an approach is likely to reduce the risk of overtreatment with immunosuppressants (10,12,29). A study protocol within the scope of this proposal was recently published by a Danish research group (44), reinforcing its current scientific and clinical relevance.

Nevertheless, with or without PtGA, rheumatologists and health care professionals should always be aware of the limitations of disease activity indices (such as noninclusion of the feet, size and relevance of involved joints to the individual patients, active swollen joints versus cold chronic scarring) and holistically consider patients' symptoms, needs, and individual circumstances (1,2,45).

Further investigation will be required to verify whether the exclusion of PtGA from the definition of remission negatively affects its long-term predictive value of important outcomes such as radiographic damage and physical function. This work is currently underway (46). A detailed examination of the potential association of PtGA with subclinical inflammation in patients otherwise in remission is also warranted.

ACKNOWLEDGMENTS

The authors thank all METEOR investigators, as well as the Merit Board for their support. We also thank Ms Manjit Saluja, who contributed substantially to the Indian data collection. We would like to acknowledge Sytske-Anne Bergstra (Leiden, Netherlands) and Rosaline van den Berg (Rotterdam, Netherlands) for their support in database management and characterization. We would like to specially acknowledge Laure Gossec (Paris, France), Maarten de Wit (Amsterdam, Netherlands), Johannes W. G. Jacobs (Utrecht, Netherlands), Paco M. J. Welsing (Utrecht, Netherlands), and Eduardo Santos (Coimbra, Portugal) for their support in developing the concept of dual-target.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Mr. Ferreira had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Ferreira, Ndosi, Duarte, van der Heijde, Machado, da Silva.

Acquisition of data. Ferreira, Carvalho.

Analysis and interpretation of data. Ferreira, Carvalho, Ndosi, Duarte, Chopra, Murphy, van der Heijde, Machado, da Silva.

REFERENCES

1. Smolen JS, Landewe R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis 2017;76:960–77.
2. Singh JA, Saag KG, Bridges SL Jr, Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Care Res (Hoboken) 2016;68:1–25.
3. Martins FM, da Silva JA, Santos MJ, Vieira-Sousa E, Duarte C, Santos H, et al. DAS28, CDAI and SDAI cut-offs do not translate the same information: results from the Rheumatic Diseases Portuguese Register Reuma.pt. Rheumatology (Oxford) 2015;54:286–91.
4. Boers M. Let's stop fooling ourselves. In RA, only ACR/EULAR criteria define remission and equate with absence of disease! Ann Rheum Dis 2016;75:e68.
5. Felson DT, Smolen JS, Wells G, Zhang B, van Tuyl LH, Funovits J, et al. American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Arthritis Rheum 2011;63:573–86.
6. Fransen J, van Riel PL. The Disease Activity Score and the EULAR response criteria. Rheum Dis Clin North Am 2009;35:745–57.
7. Aletaha D, Smolen J. The Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI): a review of their usefulness and validity in rheumatoid arthritis. Clin Exp Rheumatol 2005;23:S100–8.
8. Aletaha D, Nell VP, Stamm T, Uffmann M, Pflugbeil S, Machold K, et al. Acute phase reactants add little to composite disease activity indices for rheumatoid arthritis: validation of a clinical activity score. Arthritis Res Ther 2005;7:R796–806.
9. Van Tuyl LH, Sadlonova M, Davis B, Flurey C, Goel N, Hewlett SE, et al. Remission in rheumatoid arthritis: working toward incorporation of the patient perspective at OMERACT 12. J Rheumatol 2016;43:203–7.
10. Ferreira RJ, Duarte C, Ndosi M, de Wit M, Gossec L, da Silva JA. Suppressing inflammation in rheumatoid arthritis: does patient global assessment blur the target? A practice-based call for a paradigm change. Arthritis Care Res (Hoboken) 2018;70:369–78.
11. Bykerk VP, Massarotti EM. The new ACR/EULAR remission criteria: rationale for developing new criteria for remission. Rheumatology (Oxford) 2012;51 Suppl 6:vi16–20.
12. Ferreira RJ, Duarte C, Ndosi M, de Wit M, Gossec L, da Silva JA. The controversy of including PGA to define remission in RA [letter]. Nat Rev Rheumatol 2018;14:245.
13. Studenic P, Radner H, Smolen JS, Aletaha D. Discrepancies between patients and physicians in their perceptions of rheumatoid arthritis disease activity. Arthritis Rheum 2012;64:2814–23.
14. Khan NA, Spencer HJ, Abda EA, Alten R, Pohl C, Ancuta C, et al. Patient's global assessment of disease activity and patient's assessment of general health for rheumatoid arthritis activity assessment: are they equivalent? Ann Rheum Dis 2012;71:1942–9.
15. Navarro-Compan V, Gherghe AM, Smolen JS, Aletaha D, Landewe R, van der Heijde D. Relationship between disease activity indices and their individual components and radiographic progression in RA: a systematic literature review. Rheumatology (Oxford) 2015;54:994–1007.
16. Svensson B, Andersson ML, Bala SV, Forslind K, Hafstrom I. Long-term sustained remission in a cohort study of patients with rheumatoid arthritis: choice of remission criteria. BMJ Open 2013;3: e003554.
17. Gul HL, Ferreira JF, Emery P. Remission in rheumatoid arthritis: is it all the same? Expert Rev Clin Pharmacol 2015;8:575–86.
18. Nikiphorou E, Radner H, Chatzidionysiou K, Desthieux C, Zabalan C, van Eijk-Hustings Y, et al. Patient global assessment in measuring disease activity in rheumatoid arthritis: a review of the literature. Arthritis Res Ther 2016;18:251.
19. Ferreira RJ, Eugenio G, Ndosi M, Silva C, Medeiros C, Duarte C, et al. Influence of the different "patient global assessment" formulations on disease activity score by different indices in rheumatoid arthritis. Clin Rheumatol 2018;37:1963–9.
20. Hirsh J, Wood P, Keniston A, Peng M, Ramaswami S, Caplan L, et al. Limited health literacy and patient confusion about rheumatoid arthritis patient global assessments and model disease states. Arthritis Care Res (Hoboken) https://doi.org/10.1002/acr.23692. E-pub ahead of print.
21. Studenic P, Smolen JS, Aletaha D. Near misses of ACR/EULAR criteria for remission: effects of patient global assessment in Boolean and index-based definitions. Ann Rheum Dis 2012;71:1702–5.
22. Vermeer M, Kuper HH, van der Bijl AE, Baan H, Posthumus MD, Brus HL, et al. The provisional ACR/EULAR definition of remission in RA: a comment on the patient global assessment criterion. Rheumatology (Oxford) 2012;51:1076–80.
23. Balogh E, Dias JM, Orr C, Mullan R, Harty L, FitzGerald O, et al. Comparison of remission criteria in a tumour necrosis factor inhibitor treated rheumatoid arthritis longitudinal cohort: patient global health is a confounder. Arthritis Res Ther 2013;15:R221.
24. Ferreira RJ, Dougados M, Kirwan J, Duarte C, de Wit M, Soubrier M, et al. Drivers of patient global assessment in patients with rheumatoid arthritis who are close to remission: an analysis of 1588 patients. Rheumatology (Oxford) 2017;56:1573–8.
25. Gossec L, Kirwan JR, de Wit M, Balanescu A, Gaujoux-Viala C, Guillemin F, et al. Phrasing of the patient global assessment in the rheumatoid arthritis ACR/EULAR remission criteria: an analysis of 967 patients from two databases of early and established rheumatoid arthritis patients. Clin Rheumatol 2018;37:1503–10.
26. Van Tuyl LH, Boers M. Rheumatoid arthritis: remission–keeping the patient experience front and centre. Nat Rev Rheumatol 2017;13:573–4.

27. Masri KR, Shaver TS, Shahouri SH, Wang S, Anderson JD, Busch RE, et al. Validity and reliability problems with patient global as a component of the ACR/EULAR remission criteria as used in clinical practice. J Rheumatol 2012;39:1139–45.
28. Wells GA, Boers M, Shea B, Brooks PM, Simon LS, Strand CV, et al. Minimal disease activity for rheumatoid arthritis: a preliminary definition. J Rheumatol 2005;32:2016–24.
29. Ferreira RJ, Ndosi M, de Wit M, Santos EJ, Duarte C, Jacobs JW, et al. Dual target strategy: a proposal to mitigate the risk of overtreatment and enhance patient satisfaction in rheumatoid arthritis. Ann Rheum Dis https://doi.org/10.1136/annrheumdis-2018-214199. E-pub ahead of print.
30. Acebes C, Andreu JL, Balsa A, Batlle E, de Toro-Santos J, Garcia Llorente F, et al. Exploring the remission concept in rheumatoid arthritis with patients and rheumatologists: time for a new approach? Clin Exp Rheumatol 2017;35:816–22.
31. Lukas C, Huizinga T, van der Heijde D. METEOR as an information technology tool to assess rheumatoid arthritis disease activity in clinical practice and improve patient outcome via tailor-made treatment. Int J Adv Rheumatol 2009;7:44–50.
32. Bergstra SA, Machado PM, van den Berg R, Landewe RB, Huizinga TW. Ten years of METEOR (an international rheumatoid arthritis registry): development, research opportunities and future perspectives. Clin Exp Rheumatol 2016;34:S87–90.
33. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum 1980;23:137–45.
34. Van der Heijde DM, van 't Hof MA, van Riel PL, van Leeuwen MA, van Rijswijk MH, van de Putte LB. Validity of single variables and composite indices for measuring disease activity in rheumatoid arthritis. Ann Rheum Dis 1992;51:177–81.
35. Fleischmann RM, van der Heijde D, Gardiner PV, Szumski A, Marshall L, Bananis E. DAS28-CRP and DAS28-ESR cut-offs for high disease activity in rheumatoid arthritis are not interchangeable. RMD Open 2017;3:e000382.
36. Sharma AK. Textbook of correlations and regression. New Delhi: Discovery Publishing House; 2005.
37. Saleem B, Brown AK, Keen H, Nizam S, Freeston J, Wakefield R, et al. Should imaging be a component of rheumatoid arthritis remission criteria? A comparison between traditional and modified composite remission scores and imaging assessments. Ann Rheum Dis 2011;70:792–8.
38. Nguyen H, Ruyssen-Witrand A, Gandjbakhch F, Constantin A, Foltz V, Cantagrel A. Prevalence of ultrasound-detected residual synovitis and risk of relapse and structural progression in rheumatoid arthritis patients in clinical remission: a systematic review and meta-analysis. Rheumatology (Oxford) 2014;53:2110–8.
39. Ferreira RJ, de Wit M, Henriques M, Pinto AF, Duarte C, Mateus E, et al. "It can't be zero!" Difficulties in completing patient global assessment in rheumatoid arthritis: a mixed methods study. Rheumatology (Oxford). In Press.
40. Jacobs JW, Ten Cate DF, van Laar JM. Monitoring of rheumatoid arthritis disease activity in individual patients: still a hurdle when implementing the treat-to-target principle in daily clinical practice. Rheumatology (Oxford) 2015;54:959–61.
41. Hifinger M, Putrik P, Ramiro S, Keszei AP, Hmamouchi I, Dougados M, et al. In rheumatoid arthritis, country of residence has an important influence on fatigue: results from the multinational COMORA study. Rheumatology (Oxford) 2016;55:735–44.
42. Putrik P, Ramiro S, Hifinger M, Keszei AP, Hmamouchi I, Dougados M, et al. In wealthier countries, patients perceive worse impact of the disease although they have lower objectively assessed disease activity: results from the cross-sectional COMORA study. Ann Rheum Dis 2016;75:715–20.
43. Harrison MJ, Boonen A, Tugwell P, Symmons DP. Same question, different answers: a comparison of global health assessments using visual analogue scales. Qual Life Res 2009;18:1285–92.
44. Jørgensen TS, Lykkegaard JJ, Hansen A, Schrøder HM, Stampe B, Sweeney AM, et al. Protocol for evaluating and implementing a pragmatic value-based healthcare management model for patients with inflammatory arthritis: a Danish population-based regional cohort and qualitative implementation study. BMJ Open 2018;8:e023915.
45. Nikiphorou E, Aletaha D, Bukhari M. Are we failing patients in our assessment of treatment failure? Rheumatology (Oxford) https://doi.org/10.1093/rheumatology/key107. E-pub ahead of print.
46. Ferreira RJ, Welsing PM, Gossec L, Jacobs JW, Machado PM, van der Heijde DM, et al. The impact of patient global assessment in the definition of remission as a predictor of long-term radiographic damage in patients with rheumatoid arthritis: protocol for an individual patient data meta-analysis. Acta Rheumatol Port 2018;43:52–60.

SUPPLEMENTARY MATERIAL

Supplementary Table S1 – Patients/Visits per country*

Country	n (%)
Bosnia and Herzegovina	2 (<0.1)
Belgium	4 (<0.1)
Brazil	184 (0.7)
Canada	33 (0.1)
China	24 (0.1)
Cyprus	31 (0.1)
Czech Republic	122 (0.4)
Spain	196 (0.7)
France	195 (0.7)
United Kingdom	1341 (4.8)
Greece	41 (0.1)
Hong Kong	7 (<0.1)
Ireland	1167 (4.2)
India	**8936 (32.2)**
Italy	**4156 (15.0)**
Japan	388 (1.4)
Republic of Korea	1 (<0.1)
Latvia	32 (0.1)
Malta	1 (<0.1)
Mexico	1186 (4.3)
Nigeria	12 (<0.1)
The Netherlands	**3296 (11.9)**
Pakistan	7 (<0.1)
Poland	5 (<0.1)
Portugal	**4373 (15.7)**
Qatar	319 (1.1)
Romania	9 (<0.1)
Russian Federation	10 (<0.1)
Ukraine	15 (0.1)
United States	888 (3.2)
South Africa	716 (2.6)
Islamic Republic of Iran	71 (0.3)

*One visit only per patient (the first visit with all Boolean criteria)

Chapter IV

THE ASSOCIATION OF PGA WITH LONG-TERM PHYSICAL FUNCTION AND RADIOGRAPHIC DAMAGE IN RA

This chapter includes 2 published and 2 submitted manuscripts

Manuscript 7

Association of seventeen definitions of remission with functional status in a large international clinical practice cohort of patients with rheumatoid arthritis.

Carvalho PD, Ferreira RJO, Landewé R, Vega-Morales D, Salomon-Escoto K, Veale DJ, Chopra A, da Silva JAP, Machado PM

J Rheumatol. 2019 May 1; doi: 10.3899/jrheum.181286.

JOURNAL'S IMPACT FACTOR:

Number of external citations*: 0

Number of self-citations*: 0

CONFERENCES PRESENTATIONS/ABSTRACTS

Conference*:* EULAR Annual Congress 2017 (Madrid, Spain). Poster.

Abstract*:* Carvalho P, Ferreira RJO, Landewé R, Vega-Morales D, Salomon-Escoto K, Veale DL, da Silva JAP, Machado P, on behalf of METEOR investigators (2017). FRI0126 Aiming for remission according to any of the rheumatoid arthritis disease activity indices is more important for physical function than the actual choice of index: a longitudinal analysis in a clinical practice setting (METEOR cohort). *Ann Rheum Dis.* 76 (Suppl 2), 528-529.

Journal's Impact Factor: 12.350

Number of external citations*: 0

Number of self-citations*: 0

OTHER SCIENTIFIC OUTPUTS

Research Grant: A competitive research grant awarded (5,520.00€) by MERIT foundation in 2011 (Machado PM as first authors)

* until 30th august 2019

Association of 17 Definitions of Remission with Functional Status in a Large Clinical Practice Cohort of Patients with Rheumatoid Arthritis

Pedro D. Carvalho, Ricardo J.O. Ferreira, Robert Landewé, David Vega-Morales, Karen Salomon-Escoto, Douglas J. Veale, Arvind Chopra, José A.P. da Silva, and Pedro M. Machado

ABSTRACT. ***Objective.*** To compare the association between different remission criteria and physical function in patients with rheumatoid arthritis followed in clinical practice.

Methods. Longitudinal data from the METEOR database were used. Seventeen definitions of remission were tested: American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) Boolean-based; Simplified/Clinical Disease Activity Index (SDAI/CDAI); and 14 Disease Activity Score (DAS)-based definitions. Health Assessment Questionnaire (HAQ) ≤ 0.5 was defined as good functional status. Associations were investigated using generalized estimating equations. Potential confounders were tested and sensitivity analyses performed.

Results. Data from 32,915 patients (157,899 visits) were available. The most stringent definition of remission was the ACR/EULAR Boolean-based definition (1.9%). The proportion of patients with HAQ ≤ 0.5 was higher for the most stringent definitions, although it never reached 100%. However, this also meant that, for the most stringent criteria, many patients in nonremission had HAQ ≤ 0.5. All remission definitions were associated with better function, with the strongest degree of association observed for the SDAI (adjusted OR 3.36, 95% CI 3.01–3.74).

Conclusion. The 17 definitions of remission confirmed their validity against physical function in a large international clinical practice setting. Achievement of remission according to any of the indices may be more important than the use of a specific index. A multidimensional approach, targeted at wider goals than disease control, is necessary to help all patients achieve the best possible functional status. (J Rheumatol First Release xxxx; doi:10.3899/jrheum.181286)

Key Indexing Terms:
RHEUMATOID ARTHRITIS DISEASE ACTIVITY DISEASE ACTIVITY SCORE REMISSION

From the Rheumatology Department, Centro Hospitalar Universitário de Coimbra, Coimbra; Rheumatology Department, Centro Hospitalar Universitário do Algarve, Faro; Health Sciences Research Unit: Nursing (UICiSA:E), Escola Superior de Enfermagem de Coimbra, Coimbra; Coimbra Institute for Clinical and Biomedical Research (iCBR), Faculty of Medicine, University of Coimbra, Coimbra, Portugal; Amsterdam Rheumatology Center, Amsterdam University Medical Center (UMC); Zuyderland Medical Center, Heerlen, the Netherlands; Hospital Universitario "Dr. José Eleuterio González"/Universidad Autónoma de Nuevo León, Monterrey, Mexico; University of Massachusetts Medical School, Rheumatology Centre, Worcester, Massachusetts, USA; Dublin Academic Medical Centre, Dublin, Ireland; Centre for Rheumatic Diseases, Pune, India; Centre for Rheumatology Research, and Medical Research Council (MRC) Centre for Neuromuscular Diseases, University College London, London; Rheumatology Department, Northwick Park Hospital, London North West University Healthcare National Health Service (NHS) Trust, London, UK.

This study was supported by a research grant from the MERIT Foundation (www.meteorfoundation.com). P.M. Machado was supported by the National Institute for Health Research (NIHR) University College London Hospitals Biomedical Research Centre. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the UK Department of Health.

P.D. Carvalho, MD, Rheumatology Department, Centro Hospitalar Universitário de Coimbra, and Rheumatology Department, Centro Hospitalar Universitário do Algarve; R.J. Ferreira, Rheumatology Department, Centro Hospitalar Universitário de Coimbra, and UICiSA:E, Escola Superior de Enfermagem de Coimbra; R. Landewé, MD, PhD, Amsterdam Rheumatology Center, and Zuyderland Medical Center; D. Vega-Morales, MD, PhD, Hospital Universitario "Dr. José Eleuterio González"/Universidad Autónoma de Nuevo León; K. Salomon-Escoto, MD, PhD, University of Massachusetts Medical School, Rheumatology Centre; D.J. Veale, MD, PhD, Dublin Academic Medical Centre; A. Chopra, MD, PhD, Centre for Rheumatic Diseases; J.A. da Silva, MD, PhD, Rheumatology Department, Centro Hospitalar Universitário de Coimbra, and iCBR, Faculty of Medicine, University of Coimbra; P.M. Machado, MD, PhD, Centre for Rheumatology Research, and MRC Centre for Neuromuscular Diseases, University College London, and Rheumatology Department, Northwick Park Hospital, London North West University Healthcare NHS Trust.

Address correspondence to Dr. P.D. Carvalho, Rheumatology Department, Centro Hospitalar Universitário do Algarve, Rua Leão Penedo, 8000-386 Faro, Portugal. E-mail: pedrodcsc@gmail.com

Accepted for publication April 6, 2019.

Significant advances in the management of rheumatoid arthritis (RA) have taken place in the last few decades, allowing the establishment of remission as the target of treatment in clinical trials, and in routine clinical practice[1,2].

In spite of the existing agreement concerning the impor-

tance of achieving remission to prevent joint destruction and functional disability, there is still no consensus regarding the definition of such a goal. Ideally, remission should represent an absence or a very low state of disease activity, and should be validated against a longterm outcome, such as physical function or radiographic progression. The stringency of such a threshold will obviously influence the percentage of patients who reach it[2,3,4,5,6,7].

Several definitions of remission have been proposed, including the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) definition and others based on composite indices such as the Disease Activity Score (DAS) with multiple variations and proposed cutoffs, the Clinical Disease Activity index (CDAI), and the Simplified Disease Activity Index (SDAI)[1,2,7].

A total of 17 definitions of remission in RA can be found in the literature, all of them validated to some extent. These definitions refer to the ACR/EULAR, CDAI, SDAI, and those definitions based on DAS and the 28-joint count DAS (DAS28); each one encompassing information on C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR) and considering or not considering patient's global assessment (PtGA)[8–15]. In addition, the newest cutoffs for DAS28 were also added to the analysis. However, in previous studies, the number of definitions compared, patient numbers, or duration of followup were limited and few reports related remission to functional status. Moreover, most previous studies came from single centers or culturally homogeneous groups and none directly compared the full list of definitions, some of which were published in the last year (e.g., newly proposed DAS28 cutoffs)[14,15].

The aim of our present study was to compare the prevalence of remission according to various criteria and to study the relationship between remission and physical function in a large multinational cohort of real-life patients with RA.

MATERIALS AND METHODS

For this study, longitudinal data from the Measurement of Efficacy of Treatment in the Era of Outcome in Rheumatology (METEOR) database were used. METEOR is a software tool, designed by and for rheumatologists, available online for free, which allows longitudinal registration of disease activity and disability measures. Data can either be entered directly on the online tool or uploaded from local electronic health record systems or registries. Details of the METEOR tool have been previously described[16,17,18]. The database used in this work included visits from June 1985 until November 2015.

Seventeen definitions of remission were tested: the ACR/EULAR Boolean-based definition of remission [tender joint count ≤ 1, swollen joint count ≤ 1, CRP ≤ 1 mg/dl, and PtGA ≤ 1 (on a 0–10 scale)], SDAI ≤ 3.3, CDAI ≤ 2.8, and the 8 definitions based on DAS/DAS28. Those 8 definitions were the DAS score < 1.6 (definition with ESR or CRP), DAS28 score < 2.6 (definition with ESR or CRP), always dichotomizing for PtGA (i.e., 3 or 4 variables). In addition, the newly suggested cutoffs were also considered: DAS28-CRP < 1.9 (calculated vs SDAI), DAS28-ESR < 2.2 (calculated vs SDAI), and DAS28–CRP < 2.4 (calculated va DAS28-ESR)[14,15]. Disability was measured by the Health Assessment Questionnaire (HAQ) and HAQ ≤ 0.5 defined as "good functional status"[19].

Associations were investigated through generalized estimating equations (GEE), using HAQ ≤ 0.5 as the dependent variable and the various remission criteria as independent variables. GEE allow the combination of multiple measurements per patient and use all available data during followup, while taking into account missing values and correcting for within-patient correlation[20]. With GEE, each visit counts as an independent assessment and is used to classify the remission status of the patient, which may change over time. However, GEE allows the use of all longitudinal data because it takes the dependency of observations (within-subject/-patient correlation) into account. Models were adjusted for potential confounders: treatment with biological disease-modifying antirheumatic drugs (bDMARD), body mass index, age, sex, smoking status, gross national income per capita, disease duration, anticitrullinated peptide antibody status, rheumatoid factor status, and presence of erosions. Sensitivity analyses were performed using sets of data limited to first visits only and to patients with no missing data for all definitions of remission. A flow chart representing the number of patients and visits taken into consideration in the various subanalyses is presented in Figure 1. The METEOR registry contains completely anonymized data that were gathered during daily practice. There is no link between the anonymized data and the original patient identity, according to current General Data Protection Regulation. Treatment, timing of followup visits, and measurements were non-protocolled. Therefore, medical ethics board approval was not required.

RESULTS

Study population. Data from 32,915 patients and 157,899 visits were available (average 6.9 ± SD 7.9 visits/per patient). The sociodemographic and clinical characteristics at the first visit are described in Table 1, for all patients and for those with information about all definitions of remission (n = 9902). Regarding treatments, 42.2% were receiving corticosteroids, 72.8% conventional synthetic DMARD, and 11.1% bDMARD. The mean HAQ was 1.0 (SD 0.8; Table 1).

Data were not available for all patients; the number of patients with valid information for each variable at the first visit is presented in Table 1.

The study population resulting from this international initiative assembled patients from different countries as presented in Supplementary Table 1 (available with the online version of this article).

Fulfillment of the definitions of remission. The most stringent definitions of remission, as observed in the first METEOR visit, were the ACR/EULAR Boolean-based definition (1.9%) and the SDAI ≤ 3.3 (6.1%). Regarding the various remission criteria based on the DAS, the percentages of first visits in remission ranged between 6.5% [for the newly proposed DAS28-CRP(3v) cutoff of 1.9] and 20.4% [for the DAS-ESR(4v) cutoff of 1.6; Table 2].

Remission data taking all visits into account are also presented in Table 2. As expected, the percentage of visits with patients in remission increased at followup. The most stringent definitions of remission in this analysis were the ACR/EULAR Boolean-based definition (4.5%) and the CDAI (13.4%). The percentage of visits in SDAI remission was 17.1%, and regarding the various remission criteria based on the DAS, the percentages of visits with patients achieving remission ranged between 15.2% [for the newly

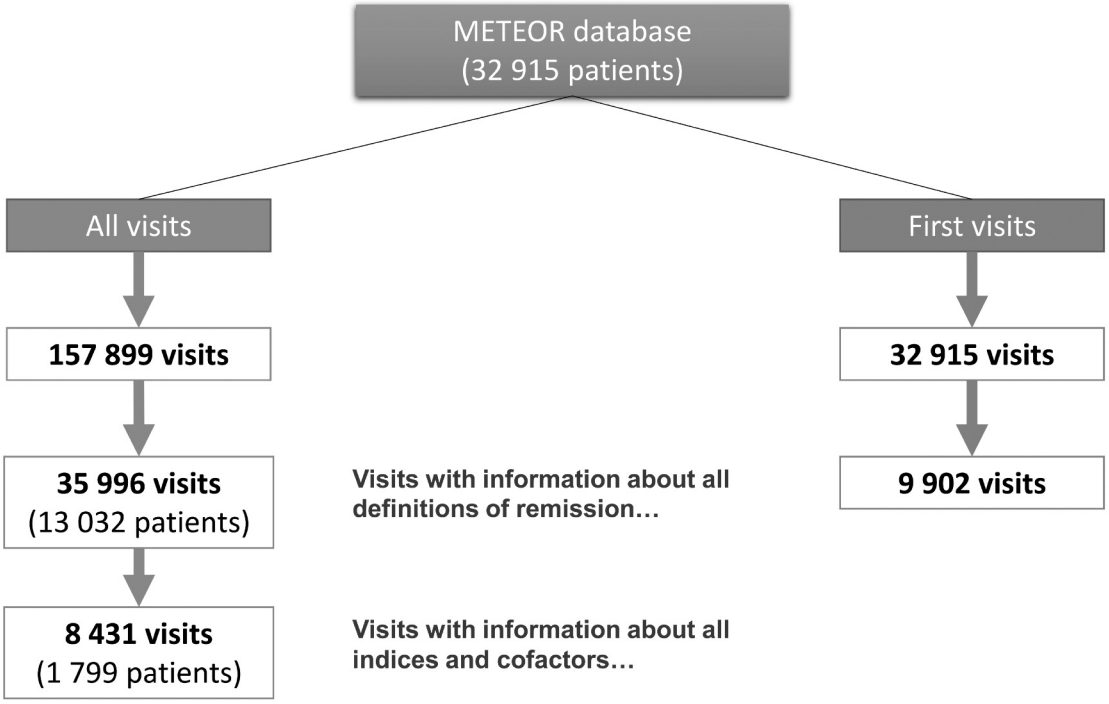


Figure 1. Flow chart representing the number of patients and visits taken into account in the analyses performed. METEOR: Measurement of Efficacy of Treatment in the Era of Outcome in Rheumatology.

Table 1. Summary of the clinical and demographic characteristics of the study population at first visit.

Characteristics	All Patients, n = 32,915		Patients with Full Information on All Definitions of Remission, n = 9902	
		N1		N2
Female sex	25,470 (78.2)	32,563	7962 (81.2)	9809
Age at visit, yrs	53.0 ± 14.8	32,089	50.4 ± 14.0	9701
Disease duration, yrs	7.2 ± 8.4	25,448	6.8 ± 7.9	8828
BMI, kg/m^2	26.5 ± 5.2	13,551	26.1 ± 5.3	4444
Smoker, current	2700 (12.5)	21,599	682 (8.3)	8182
RF-positive	19,739 (73.3)	26,924	7069 (77.4)	9137
ACPA-positive	11,229 (70.3)	15,981	3651 (74.3)	4916
Erosions	8611 (53.7)	16,027	2693 (55.9)	4820
Treatment with bDMARD	3660 (11.1)	32,915	889 (9.0)	9902
TJC28, n	8.6 ± 9.3	29,908	11.2 ± 9.8	9902
SJC28, n	4.0 ± 5.1	30,865	5.0 ± 5.5	9902
PtGA, cm	4.6 ± 2.6	24,764	5.2 ± 2.3	9902
PGA, cm	4.1 ± 2.2	20,406	4.3 ± 2.1	9902
HAQ	1.0 ± 0.8	12,176	± 0.8	3195

Values are n (%) or mean ± SD. ACPA: anticitrullinated peptide antibodies; BMI: body mass index; bDMARD: biological disease-modifying antirheumatic drugs; HAQ: Health Assessment Questionnaire; N1 and N2: no. patients with information available; PtGA: patient's global assessment; PGA: physician's global assessment; RF: rheumatoid factor; SJC28: 28-joint swollen joint count; TJC28: 28-joint tender joint count.

proposed DAS28-ESR(3v) cutoff of 2.2] and 39.1% [for the DAS-CRP(3v) cutoff of 1.6].

Remission data regarding the subset of visits with information on all definitions of remission are presented in Supplementary Table 2 (available with the online version of this article). Results for this subset of patients were similar to those described above.

Proportion of visits with patients with good functional status among visits with and without disease activity remission status. As presented in Table 3, at first visit, the proportion

Table 2. Visits in remission according to different definitions of remission*.

Definition of Remission		Patients in Remission at First METEOR Visit, n (%)	N1	Visits in Remission Taking All Visits into Account, n (%)	N2
ACR/EULAR Boolean-based		279 (1.9)	14,696	2465 (4.5)	55,261
SDAI ≤ 3.3		705 (6.1)	11,562	7072 (17.1)	41,420
CDAI ≤ 2.8		1188 (7.6)	15,682	9579 (13.4)	71,790
DAS-CRP < 1.6	4v	2093 (16.0)	13,067	19,481 (38.6)	50,517
	3v	2688 (15.5)	17,352	23,924 (39.1)	61,214
DAS-ESR < 1.6	4v	3699 (20.4)	18,170	29,256 (31.7)	92,164
	3v	4238 (18.6)	22,780	33,774 (30.4)	111,149
DAS28-CRP < 2.6	4v	2326 (15.8)	14,696	19,252 (34.8)	55,261
	3v	3097 (16.3)	19,049	24,742 (37.5)	65,944
DAS28-ESR < 2.6	4v	3295 (16.1)	20,497	24,895 (25.2)	98,629
	3v	3765 (14.9)	25,235	28,647 (24.4)	117,404
DAS28-CRP < 1.9**	4v	1020 (6.9)	14,696	9328 (16.9)	55,261
	3v	1235 (6.5)	19,049	11,503 (17.4)	65,944
DAS28-ESR < 2.2**	4v	2032 (9.9)	20,497	15,922 (16.1)	98,629
	3v	2032 (8.8)	25,235	17,875 (15.2)	117,404
DAS28-CRP < 2.4**	4v	1960 (13.3)	14,696	16,716 (30.2)	55,261
	3v	2657 (13.9)	19,049	21,500 (32.5)	65,944

* Results at the first METEOR visit and taking all visits into account. ** DAS28 formulae with the newly suggested cutoffs [DAS28-CRP < 1.9 (calculated vs SDAI), DAS28-ESR < 2.2 (calculated vs SDAI), and DAS28-CRP < 2.4 (calculated vs DAS28-ESR)]. ACR: American College of Rheumatology; EULAR: European League Against Rheumatism; CDAI: Clinical Disease Activity Index; CRP: C-reactive protein; DAS: Disease Activity Score; DAS28: 28-joint count DAS; ESR: erythrocyte sedimentation rate; METEOR: Measurement of Efficacy of Treatment in the Era of Outcome in Rheumatology; N1 and N2: no. visits with information available; SDAI: Simplified Disease Activity Index; 4v: 4 variables.

Table 3. Visits in good functional status (HAQ ≤ 0.5) according to remission status.

Definition of Remission		Remission, at First METEOR Visit Yes**	No**	Remission, Taking All Visits into Account Yes**	No**
ACR/EULAR Boolean-based		182 (88.8)	1868 (29.3)	1556 (87.0)	10,897 (34.1)
SDAI ≤ 3.3		403 (81.7)	827 (21.6)	4011 (78.1)	5005 (25.7)
CDAI ≤ 2.8		606 (80.5)	1364 (25.1)	4900 (78.5)	6775 (27.4)
DAS-CRP < 1.6	4v	814 (58.6)	780 (20.5)	7826 (59.1)	3253 (19.3)
	3v	818 (54.5)	830 (21.1)	7836 (56.4)	3583 (20.7)
DAS-ESR < 1.6	4v	1191 (60.8)	1211 (23.1)	9169 (63.2)	5105 (22.6)
	3v	1158 (56.7)	1314 (24.1)	8970 (60.4)	5693 (24.3)
DAS28-CRP < 2.6	4v	1056 (64.6)	994 (20.1)	8316 (62.8)	4137 (20.2)
	3v	1091 (58.8)	1024 (20.5)	8512 (57.7)	4301 (21.3)
DAS28-ESR < 2.6	4v	1154 (67.5)	1863 (25.8)	8292 (68.1)	7828 (26.5)
	3v	1067 (60.5)	2041 (27.0)	7711 (62.5)	8851 (28.7)
DAS28-CRP < 1.9*	4v	567 (75.3)	1483 (25.4)	5002 (74.8)	7451 (27.6)
	3v	550 (68.2)	1565 (25.9)	4778 (65.8)	8035 (29.1)
DAS28-ESR < 2.2*	4v	712 (69.3)	2305 (29.2)	5616 (72.3)	10,504 (30.9)
	3v	611 (61.1)	2497 (30.1)	4921 (64.9)	11,641 (32.7)
DAS28-CRP < 2.4*	4v	941 (67.4)	1109 (21.4)	7583 (65.5)	4870 (22.0)
	3v	978 (61.2)	1137 (21.6)	7737 (60.2)	5076 (23.0)

Values are n (%). * DAS28 formulae with the newly suggested cutoffs [DAS28-CRP < 1.9 (calculated vs SDAI), DAS28-ESR < 2.2 (calculated vs SDAI), and DAS28-CRP < 2.4 (calculated vs DAS28-ESR)]. ** Percentages presented in each column are independent (not complementary) of the next-side column. ACR: American College of Rheumatology; EULAR: European League Against Rheumatism; CDAI: Clinical Disease Activity Index; CRP: C-reactive protein; DAS: Disease Activity Score; DAS28: 28-joint count DAS; ESR: erythrocyte sedimentation rate; HAQ: Health Assessment Questionnaire; METEOR: Measurement of Efficacy of Treatment in the Era of Outcome in Rheumatology; SDAI: Simplified Disease Activity Index; 4v: 4 variables.

of visits with HAQ ≤ 0.5 among patients in remission was higher for the most stringent definitions (88.8% for ACR/EULAR Boolean-based, 81.7% for SDAI, 80.5% for CDAI). A significant proportion of visits with patients in nonremission had HAQ ≤ 0.5 (e.g., 29.3% for ACR/EULAR Boolean-based definition, 21.6% of patients without SDAI remission, and 25.1% of patients without CDAI remission). The prevalence of good functional status in visits with

patients fulfilling DAS/DAS28 remission definitions ranged from 54.5% [for DAS-CRP(3v) < 1.6] to 75.3% [for DAS28-CRP(4v) < 1.9]. Among visits with patients not fulfilling DAS/DAS28 remission, the proportion of patients with good functional status ranged from 20.1% [for patients not fulfilling DAS28-CRP(4v) < 2.6] to 30.1% [for patients not fulfilling DAS28-ESR(3v) < 2.2]. Similar results were obtained when all visits in the database were considered (Table 3) and when only patients with information available for all definitions of remission were considered (Supplementary Table 3, available with the online version of this article).

A significant proportion of patients in remission reported HAQ scores > 0.5 at the same visit (11.2–45.5%) and a significant proportion of patients in not in remission had HAQ scores ≤ 0.5 (19.3–34.1%). The proportion of patients not in remission who had HAQ ≤ 0.5 was higher for the most stringent definitions (Table 3).

Associations between remission and good functional status. The strongest association between remission and good functional state was observed for the SDAI definition of remission (OR 3.774, 95% CI 3.492–4.078). Results were not divergent through the other definitions (Table 4), with the majority of 95% CI for the OR overlapping. Similar results were obtained when the model was adjusted for significant cofactors (SDAI adjusted OR 3.357, 95% CI 3.012–3.742). Remission criteria based on DAS were more strongly associated with good functional status when 4v definitions were used (OR 4v between 2.778 and 3.365) compared to when 3v definitions were considered (OR 3v between 2.204 and 2.809). When CI of similar scores were compared, the lower limit of the OR for the 4v definition was always higher than the higher limit of the comparable 3v definition. A similar tendency was observed when adjusted OR were compared; however, some overlapping CI were observed.

When analyzing only visits with information available for all definitions of remission (Table 5), the SDAI definition of remission remained the most strongly associated with good functional status (OR 3.629, 95% CI 3.338–3.945). Once again, DAS-based remission criteria presented a trend to be more associated with good functional status when 4v models were considered (OR 4v between 2.769 and 3.406), in comparison to 3v models (OR 3v between 2.248 and 3.016). However, overlaps between CI were observed for some definitions. In this analysis, when OR were adjusted for significant cofactors, the strongest association between remission and good functional status was observed for DAS-CRP(4v) < 1.6 (OR 3.793, 95% CI 3.354–4.289), followed by SDAI (OR 3.549, 95% CI 3.107–4.053; Table 4).

Stringency of the newly proposed DAS28 remission cutoffs. As expected, the new cutoffs for DAS28 remission (DAS28-CRP < 1.9 and DAS28-ESR < 2.2) were associated with a lower percentage of visits in remission (range between 6.5% and 9.9% vs 14.9% and 16.3%, respectively, at first visit; Table 2). However, the cutoffs were still less stringent than the ACR/EULAR Boolean-based or SDAI criteria (1.9% and 6.1%, respectively). Similar results were obtained when all visits were taken into account (Table 2). Their degree of

Table 4. Longitudinal associations between good functional status (dependent variable) and remission (independent variable)*.

Definition of Remission		HAQ ≤ 0.5			
		N	Univariable OR (95% CI)	N	Adjusted OR** (95% CI)
ACR/EULAR Boolean-based		33,709	2.973 (2.730–3.236)	16,247	2.555 (2.259–2.889)
SDAI ≤ 3.3		24,633	3.774 (3.492–4.078)	12,499	3.357 (3.012–3.742)
CDAI ≤ 2.8		30,977	3.659 (3.417–3.920)	15,137	3.152 (2.855–3.481)
DAS-CRP < 1.6	4v	30,097	3.086 (2.913–3.270)	15,421	3.211 (2.935–3.513)
	3v	31,186	2.740 (2.594–2.894)	15,918	2.778 (2.555–3.022)
DAS-ESR < 1.6	4v	37,104	3.104 (2.950–3.266)	18,520	2.956 (2.739–3.189)
	3v	38,327	2.684 (2.557–2.817)	19,066	2.630 (2.444–2.830)
DAS28-CRP < 2.6	4v	33,709	3.365 (3.185–3.554)	16,247	3.292 (3.027–3.581)
	3v	34,894	2.809 (2.670–2.956)	16,751	2.803 (2.589–3.036)
DAS28-ESR < 2.6	4v	41,748	3.030 (2.886–3.182)	19,577	2.838 (2.635–3.056)
	3v	43,166	2.443 (2.332–2.559)	20,162	2.338 (2.176–2.511)
DAS28-CRP < 1.9***	4v	33,709	3.050 (2.874–3.237)	16,247	2.799 (2.571–3.048)
	3v	34,894	2.400 (2.274–2.533)	16,751	2.256 (2.089–2.436)
DAS28-ESR < 2.2***	4v	41,748	2.778 (2.630–2.933)	19,577	2.486 (2.294–2.693)
	3v	43,166	2.204 (2.090–2.326)	20,162	1.989 (1.838–2.151)
DAS28-CRP < 2.4***	4v	33,709	3.296 (3.119–3.483)	16,247	3.181 (2.925–3.459)
	3v	34,894	2.740 (2.602–2.885)	16,751	2.643 (2.443–2.860)

* Results for the entire set of visits. ** Adjusted OR for significant cofactors (age at visit, body mass index, female sex, rheumatoid factor positivity, presence of erosions, treatment with biologics). *** DAS28 formulae with the newly suggested cutoffs [DAS28-CRP < 1.9 (calculated vs SDAI), DAS28-ESR < 2.2 (calculated vs SDAI), and DAS28-CRP < 2.4 (calculated vs DAS28-ESR)]. ACR: American College of Rheumatology; EULAR: European League Against Rheumatism; CDAI: Clinical Disease Activity Index; CRP: C-reactive protein; DAS: Disease Activity Score; DAS28: 28-joint count DAS; ESR: erythrocyte sedimentation rate; HAQ: Health Assessment Questionnaire; SDAI: Simplified Disease Activity Index; 4v: 4 variables.

Table 5. Longitudinal associations between good functional status (dependent variable) and remission (independent variable)*.

Definition of Remission		HAQ ≤ 0.5	
		OR (95% CI), n = 20,808 Visits; 5548 Patients	Adjusted OR** (95% CI), n = 8 431 Visits; 1799 Patients
ACR/EULAR Boolean-based		2.657 (2.395–2.947)	2.452 (2.087–2.881)
SDAI ≤ 3.3		3.629 (3.338–3.945)	3.549 (3.107–4.053)
CDAI ≤ 2.8		3.584 (3.297–3.896)	3.428 (3.007–3.908)
DAS-CRP < 1.6	4v	3.396 (3.160–3.649)	3.793 (3.354–4.289)
	3v	3.016 (2.816–3.230)	3.342 (2.977–3.751)
DAS-ESR < 1.6	4v	3.233 (3.015–3.467)	3.439 (3.062–3.862)
	3v	2.798 (2.615–2.994)	3.026 (2.706–3.383)
DAS28-CRP < 2.6	4v	3.406 (3.173–3.657)	3.489 (3.102–3.925)
	3v	2.866 (2.680–3.065)	3.052 (2.729–3.413)
DAS28-ESR < 2.6	4v	3.112 (2.893–3.348)	2.963 (2.636–3.331)
	3v	2.487 (2.323–2.663)	2.483 (2.217–2.781)
DAS28-CRP < 1.9***	4v	2.938 (2.729–3.163)	2.966 (2.636–3.336)
	3v	2.276 (2.128–2.434)	2.371 (2.127–2.645)
DAS28-ESR < 2.2***	4v	2.769 (2.560–2.995)	2.519 (2.223–2.855)
	3v	2.248 (2.082–2.427)	2.059 (1.823–2.324)
DAS28-CRP < 2.4***	4v	3.311 (3.083–3.556)	3.368 (2.990–3.795)
	3v	2.704 (2.530–2.889)	2.815 (2.523–3.142)

* Results considering only visits with data for all definitions of remission. ** Adjusted for age at visit, body mass index, female sex, rheumatoid factor positivity, presence of erosions, treatment with biologics. *** DAS28 formulae with the newly suggested cutoffs [DAS28-CRP < 1.9 (calculated vs SDAI), DAS28-ESR < 2.2 (calculated vs SDAI), and DAS28-CRP < 2.4 (calculated DAS28-ESR)]. ACR: American College of Rheumatology; EULAR: European League Against Rheumatism; CDAI: Clinical Disease Activity Index; CRP: C-reactive protein; DAS: Disease Activity Score; DAS28: 28-joint count DAS; ESR: erythrocyte sedimentation rate; HAQ: Health Assessment Questionnaire; SDAI: Simplified Disease Activity Index; 3v: 3 variables; 4v: 4 variables.

association with good functional status (OR between 2.2 and 3.2) was similar to the older cutoffs (OR between 2.4 and 3.4).

DISCUSSION

This study confirmed the association between various remission definitions and physical function in a large international clinical practice setting. We found that the most stringent definition of remission was the ACR/EULAR Boolean-based definition and confirmed that the newly proposed DAS28 remission cutoffs (DAS28-CRP < 1.9 and DAS28-ESR < 2.2) result in remission rates that are closer to the most stringent definitions. The proportion of patients with good functional status among those in remission was higher for the most stringent definitions. However, being in clinical remission was not always equivalent to having good functional status. Conversely, some patients not in remission had good functional status. The proportion of patients with good functional status among patients not in remission was typically higher when the most stringent definitions of remission were used.

The strongest degree of association between remission and good functional status was observed for the SDAI. However, differences between the various definitions were generally minor. Results were highly consistent in all the analyses performed, whether using first visits only, all visits, or only visits with complete data for all the 17 definitions of remission.

ACR/EULAR, CDAI, and SDAI remission criteria had already been described as the most stringent definitions of remission. In a German database with 6864 patients with RA, the percentages of remission according to DAS28-ESR(4v) < 2.6, SDAI and ACR/EULAR Boolean-based definitions were 28.1%, 10.8%, and 6.9%, respectively[21]. CDAI criteria were not evaluated in that study. We found that CDAI remission criteria were more stringent than SDAI (when all visits were taken into account). In a paradigmatic clinical trial (the BeSt study), in which 508 RA patients with early disease were included, ACR/EULAR, CDAI, and SDAI remission criteria also classified a lower proportion of patients as being in remission compared to the indices based on DAS28. This study also demonstrated a positive association between remission and good functional status defined by a HAQ ≤ 0.5[12].

A higher proportion of patients in good functional status was observed for the most stringent definitions (ACR/EULAR Boolean-based, SDAI ≤ 3.3, and CDAI ≤ 2.8). A tendency to a stronger association between remission and good functional status was observed for the SDAI definition. The OR obtained with different definitions were similar and CI overlapped. Remission criteria based on DAS presented a trend to be a stronger predictor of good functional status

when the 4v definitions were used. This was confirmed by sensitivity analyses and probably reflects the effect of functional status upon the PtGA score, included in the 4v definitions. This is in line with the observation by Ferreira, *et al*[22] that PtGA in patients with RA is strongly associated with disease effect factors, such as function, fatigue, pain, and anxiety, and only weakly with disease activity. This is even more pronounced in patients who keep high PtGA scores in the absence of overt signs of inflammation.

As mentioned, despite the clear association between the two, remission does not always mean good functional status. Some previous studies suggest that coping strategies may contribute to the dissociation between remission and good functional status observed in a sizeable proportion of patients. Patients with effective coping tend to report a less-severe functional impairment in RA[23] and in other rheumatic diseases[24].

The new remission definitions for DAS28[14] confirmed in this setting a tendency to have a stronger association with good functional status than the previous ones. This may suggest that these definitions should be preferable. However, the argument is complex. When Thiele, *et al* compared patients with RA to a randomly matched sample from the general German population, they found that patients fulfilling DAS28-ESR(4v) remission criteria had a functional status identical to the matched controls, but those who fulfilled SDAI or Boolean-based remission criteria had a considerably better functional status than the matched controls[21]. This suggests that the new Boolean-based and SDAI criteria may select supernormal patients that are not only free from active RA but also from other comorbid conditions, and who have the most effective coping strategies. Because activity indices are used to guide clinical treatment decisions, it is important that clinicians are aware of this issue, to avoid overtreatment[25]. Patients with comorbid conditions, including other musculoskeletal conditions such as osteoarthritis and fibromyalgia, may never be able to meet the most stringent remission criteria, even if RA is brought under absolute control and has no functional effect of its own[26]. Patients with comorbidities, who represent the norm in clinical practice, will benefit more from guided treatments to the specific comorbidity than from immunosuppressive agents.

Our study included data from 32,915 patients and 157,899 visits from all around the world. This makes it the largest study ever performed addressing the current aims, to our knowledge, thanks to the METEOR multinational collaborative initiative. Further, 17 definitions of remission were analyzed and compared, which is also unprecedented. The statistical methods used allowed us to analyze a large number of timepoints simultaneously, while adjusting for within-patient correlation. Because data were collected from patients followed in regular clinics, there was a significant number of missing data. To account for possible selection bias, extensive sensitivity analyses were performed. In general, results were consistent across all the analyses. However, some limitations may also be considered, including the heterogeneity of the population, which may implicate genetic, social, and demographic differences that might have influenced the results in a manner that we cannot estimate or account for. The remission criteria studied in this paper and even HAQ were developed mostly in white patients and their validity in such different populations was not clearly established yet. When comparing results of different remission definitions, readers should be aware that a certain overlap between groups is present, as a patient may be simultaneously in remission according to different definitions. As patients were treated according to local standard of care, different treatments could influence remission rates. We considered biologic treatment as the main possible treatment confounder, and adjustment for biologic treatment was included in the multivariable models, yielding results similar to the unadjusted models; however, the effect of other treatments was not analyzed in this study.

The various remission definitions confirmed their association with physical function in a large prospective international clinical practice setting. In spite of this, importantly, many patients not in remission have good functional status, while being in clinical remission does not equate to having good functional status. A multidimensional approach should be taken to help patients achieve this functional goal. Achievement of remission according to any of the indices may be more important than the selection of a specific one.

ACKNOWLEDGMENT

We thank the Merit Board for all its support, and all METEOR investigators. We especially acknowledge Sytske-Anne Bergstra (Leiden, the Netherlands) and Rosaline van den Berg (Leiden, the Netherlands) for their support in database management.

DATA AVAILABILITY

The datasets generated and/or analyzed during the current study are not publicly available because of privacy policies but are available from the corresponding author on reasonable request.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

REFERENCES

1. Ramiro S, Machado P, Singh JA, Landewe RB, da Silva JA. Applying science in practice: The optimization of biological therapy in rheumatoid arthritis. Arthritis Res Ther 2010;12:220.
2. Mierau M, Schoels M, Gonda G, Fuchs J, Aletaha D, Smolen JS. Assessing remission in clinical practice. Rheumatology 2007;46:975-9.
3. Ranganath VK, Khanna D, Paulus HE. ACR remission criteria and response criteria. Clin Exp Rheumatol 2006;6 Suppl 43:S-14-21.
4. Bergman MJ. Assessing adequate treatment response in patients with rheumatoid arthritis. Clin Ther 2009;31:1219-31.
5. Makinen H, Hannonen P, Sokka T. Definitions of remission for rheumatoid arthritis and review of selected clinical cohorts and randomised clinical trials for the rate of remission. Clin Exp Rheumatol 2006;6 Suppl 43:S-22-8.

6. Martins FM, da Silva JA, Santos MJ, Vieira-Sousa E, Duarte C, Santos H, et al. DAS28, CDAI and SDAI cut-offs do not translate the same information: Results from the Rheumatic Diseases Portuguese Register Reuma.pt. Rheumatology 2015;54:286-91.
7. van Tuyl LH, Vlad SC, Felson DT, Wells G, Boers M. Defining remission in rheumatoid arthritis: Results of an initial American College of Rheumatology/European League Against Rheumatism consensus conference. Arthritis Rheum 2009;61:704-10.
8. Zhang B, Combe B, Rincheval N, Felson DT. Validation of ACR/EULAR definition of remission in rheumatoid arthritis from ra practice: the ESPOIR cohort. Arthritis Res Ther 2012;14:R156.
9. Svensson B, Andersson ML, Bala SV, Forslind K, Hafström I; BARFOT study group. Long-term sustained remission in a cohort study of patients with rheumatoid arthritis: choice of remission criteria. BMJ Open 2013;3:e003554.
10. Ajeganova S, Huizinga T. Sustained remission in rheumatoid arthritis: latest evidence and clinical considerations. Ther Adv Musculoskelet Dis 2017;9:249-62.
11. van Tuyl LH, Felson DT, Wells G, Smolen J, Zhang B, Boers M; American College of Rheumatology; European League against Rheumatism Committee to Define Remission for Clinical Trials. Evidence for predictive validity of remission on long-term outcome in rheumatoid arthritis: a systematic review. Arthritis Care Res 2010;62:108-17.
12. Klarenbeek NB, Koevoets R, van der Heijde DM, Gerards AH, Ten Wolde S, Kerstens PJ, et al. Association with joint damage and physical functioning of nine composite indices and the 2011 ACR/EULAR remission criteria in rheumatoid arthritis. Ann Rheum Dis 2011;70:1815-21.
13. Einarsson JT, Geborek P, Saxne T, Kristensen LE, Kapetanovic MC. Sustained remission improves physical function in patients with established rheumatoid arthritis, and should be a treatment goal: a prospective observational cohort study from southern Sweden. J Rheumatol 2016;43:1017-23.
14. Fleischmann R, van der Heijde D, Koenig AS, Pedersen R, Szumski A, Marshall L, et al. How much does Disease Activity Score in 28 joints ESR and CRP calculations underestimate disease activity compared with the Simplified Disease Activity Index? Ann Rheum Dis 2015;74:1132-7.
15. Fleischmann RM, van der Heijde D, Gardiner PV, Szumski A, Marshall L, Bananis E. DAS28-CRP and DAS28-ESR cut-offs for high disease activity in rheumatoid arthritis are not interchangeable. RMD Open 2017;3:e000382.
16. Bergstra SA, Machado PM, van den Berg R, Landewé RB, Huizinga TW. Ten years of METEOR (an international rheumatoid arthritis registry): development, research opportunities and future perspectives. Clin Exp Rheumatol 2016;5 Suppl 101:S87-S90.
17. Bergstra SA, Winchow LL, Murphy E, Chopra A, Salomon-Escoto K, Fonseca JE, et al. How to treat patients with rheumatoid arthritis when methotrexate has failed? The use of a multiple propensity score to adjust for confounding by indication in observational studies. Ann Rheum Dis 2019;78:25-30.
18. Bergstra SA, Branco JC, Vega-Morales D, Salomon-Escoto K, Govind N, et al. Inequity in access to BDMARD care and how it influences disease outcomes across countries worldwide: Results from the METEOR-registry. Ann Rheum Dis 2018;77:1413-20.
19. Wells GA, Boers M, Shea B, Brooks PM, Simon LS, Strand CV, et al. Minimal disease activity for rheumatoid arthritis: a preliminary definition. J Rheumatol 2005;32:2016-24.
20. Twisk JW. Longitudinal data analysis. A comparison between generalized estimating equations and random coefficient analysis. Eur J Epidemiol 2004;19:769-76.
21. Thiele K, Huscher D, Bischoff S, Spathling-Mestekemper S, Backhaus M, Aringer M, et al; German Collaborative Arthritis Centres. Performance of the 2011 ACR/EULAR preliminary remission criteria compared with DAS28 remission in unselected patients with rheumatoid arthritis. Ann Rheum Dis 2013;72:1194-9.
22. Ferreira RJ, Duarte C, Ndosi M, de Wit M, Gossec L, da Silva JA. Suppressing inflammation in rheumatoid arthritis: does patient global assessment blur the target? A practice-based call for a paradigm change. Arthritis Care Res 2018;70:369-78.
23. Flurey CA, Hewlett S, Rodham K, White A, Noddings R, Kirwan JR. Coping strategies, psychological impact, and support preferences of men with rheumatoid arthritis: a multicentre survey. Arthritis Care Res 2018;70:851-60.
24. Peláez-Ballestas I, Boonen A, Vázquez-Mellado J, Reyes-Lagunes I, Hernández-Garduño A, Goycochea MV, et al; REUMAIMPACT group. Coping strategies for health and daily-life stressors in patients with rheumatoid arthritis, ankylosing spondylitis, and gout: STROBE-compliant article. Medicine 2015;94:e600.
25. Smolen JS, Landewe R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis 2017;76:960-77.
26. Vega-Morales D, Lozano-Plata LI, Esquivel-Valerio JA. The effect size of fibromyalgia on PG-VAS in rheumatoid arthritis patients. Adjustment proposal in DAS28-ESR: letter to the editor regarding Challa, D.N.V., Crowson, C.S. & Davis, J.M. Rheumatol Ther 2017;4:515-17.

Association of seventeen definitions of remission with functional status in a large international clinical practice cohort of patients with rheumatoid arthritis (METEOR cohort)

Supplementary table 1. Country of origin at first visit and taking all visits in account.

Country of origin	Number of patients at first visit (%)
India	10687 (32.5)
The Netherlands	7507 (22.8)
Portugal	4757 (14.5)
United Kingdom	1966 (6.0)
Mexico	1902 (5.8)
Ireland	1642 (5.0)
United States	1303 (4.0)
Other countries	3151 (9.3)
Total	32915 (100.0)

Supplementary table 2. Number and percentage of visits in remission according to different definitions of remission.*

Definition of remission		At first METEOR visit (Total =9902) n (%)	Taking all visits into account (Total =35996) n (%)
ACR/EULAR Boolean-based		92 (0.9)	1433 (4.0)
SDAI ≤3.3		508 (5.1)	6166 (17.1)
CDAI ≤2.8		503 (5.1)	6082 (16.9)
DAS-CRP-4v <1.6	4v	1405 (14.2)	14315 (39.8)
	3v	1463 (14.8)	14621 (40.6)
DAS-ESR-4v <1.6	4v	1224 (12.4)	12586 (35.0)
	3v	1254 (12.7)	12673 (35.2)
DAS28-CRP <2.6	4v	1156 (11.7)	12669 (35.2)
	3v	1303 (13.2)	13872 (38.5)
DAS28-ESR <2.6	4v	850 (8.6)	9287 (25.8)
	3v	899 (9.1)	9349 (26.0)
DAS28-CRP <1.9**	4v	482 (4.9)	6178 (17.2)
	3v	495 (5.0)	6483 (18.0)
DAS28-ESR <2.2**	4v	534 (5.4)	5962 (16.6)
	3v	545 (5.5)	5836 (16.2)
DAS28-CRP <2.4**	4v	977 (9.9)	11059 (30.7)
	3v	1103 (11.1)	12055 (33.5)

CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; METEOR, Measurement of Efficacy of Treatment in the Era of Outcome in Rheumatology; SDAI, Simplified Disease Activity Index; vs, versus. *Considering only visits with information on all definitions of remission. **DAS28 formulae with the newly suggested cut-offs [DAS28-CRP<1.9 (calculated versus SDAI), DAS28-ESR<2.2 (calculated versus SDAI) and DAS28-CRP<2.4 (calculated versus DAS28-ESR)].

Supplementary table 3. Visits with good functional status (HAQ≤0.5) according to remission status in different definitions.*

Definition of remission		Remission, at first METEOR visit		Remission, taking all visits into account	
		Yes	No	Yes	No
ACR/EULAR Boolean-based		48 (87.3)	840 (26.8)	911 (86.8)	6733 (34.1)
SDAI ≤3.3		277 (81.7)	611 (21.4)	3498 (77.6)	4146 (25.4)
CDAI ≤2.8		266 (81.3)	622 (21.7)	3428 (77.8)	4216 (25.7)
DAS-CRP <1.6	4v	508 (56.8)	380 (16.5)	5748 (58.6)	1896 (17.2)
	3v	500 (53.8)	388 (17.1)	5602 (56.4)	2042 (18.8)
DAS-ESR <1.6	4v	452 (58.2)	436 (18.0)	5247 (61.5)	2397 (19.5)
	3v	437 (55.1)	451 (18.8)	5037 (58.9)	2607 (21.3)
DAS28-CRP <2.6	4v	467 (62.9)	421 (17.2)	5379 (61.7)	2265 (18.7)
	3v	470 (56.5)	418 (17.7)	5367 (56.8)	2277 (20.0)
DAS28-ESR <2.6	4v	353 (67.4)	535 (20.0)	4240 (67.2)	3404 (23.5)
	3v	326 (58.7)	562 (21.3)	3843 (61.4)	3801 (26.1)
DAS28-CRP <1.9**	4v	241 (77.0)	647 (22.4)	3268 (73.7)	4376 (26.7)
	3v	206 (65.2)	682 (23.7)	2984 (64.2)	4660 (28.8)
DAS28-ESR <2.2**	4v	224 (68.7)	664 (24.1)	2926 (71.9)	4718 (28.2)
	3v	202 (61.4)	686 (23.9)	2494 (64.4)	5150 (30.4)
DAS28-CRP <2.4**	4v	419 (66.0)	469 (18.3)	4934 (64.4)	2710 (20.6)
	3v	414 (58.5)	474 (19.1)	4876 (59.0)	2768 (22.1)

CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; METEOR, Measurement of Efficacy of Treatment in the Era of Outcome in Rheumatology; SDAI, Simplified Disease Activity Index; vs, versus. *Considering only visits with data on all definitions of remission DAS28 formulae with the newly suggested cut-offs [DAS28-CRP<1.9 (calculated versus SDAI), DAS28-ESR<2.2 (calculated versus SDAI) and DAS28-CRP<2.4 (calculated versus DAS28-ESR)]. **Percentages presented in each column are independent (not complementary) of the next-side column.

Manuscript 8

Patient global assessment and radiographic progression in early arthritis: 3-year results from the ESPOIR cohort.

Ferreira RJO, Fautrel B, Saraus A, Gaujoux-Viala C, Rat A-C, Guillemin F, da Silva JAP, Dougados M, Gossec L

(Submitted)

Patient global assessment and radiographic progression in early arthritis: 3-year results from the ESPOIR cohort

Authors:

Ricardo J. O. Ferreira, RN, MsC[1] Bruno Fautrel, MD, PhD[2] Alain Saraux, MD, PhD [3] Cécile Gaujoux-Viala, MD, PhD [4] Anne-Christine Rat, MD, PhD [5] Francis Guillemin, MD, PhD [6] José A. P. da Silva, MD, PhD [7] Maximne Dougados, MD, PhD [8] Laure Gossec MD, PhD [9]

1 – Department of Rheumatology, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal; Health Sciences Research Unit: Nursing (UICiSA:E), Centro Hospitalar e Universitário de Coimbra affiliate, Coimbra, Portugal. ORCID: https://orcid.org/0000-0002-2517-0247

2 – Sorbonne Université, Institut Pierre Louis d'Epidémiologie et de Santé Publique, INSERM, , Paris, France; CRI IMIDIATE Clinical Research Network; Department of rheumatology, AP-HP, Pitié Salpêtrière Hospital, Paris, France. ORCID: https://orcid.org/0000-0001-8845-4274

3 – Department of Rheumatology, CHU Brest, Brest, France; UMR1227, Lymphocytes B et Autoimmunité, Inserm, Université de Bretagne occidentale (UBO), Brest, France. ORCID: https://orcid.org/0000-0002-8454-7067

4 – Department of Rheumatology, Nîmes University Hospital; IDESP, Montpellier University, Nîmes, France.

5 – Université de Lorraine, EA 4360 APEMAC, Nancy France; Department of Rheumatology, CHU Caen, Caen, France. ORCID: https://orcid.org/0000-0003-2463-772X

6 – Université de Lorraine, EA 4360 APEMAC, Nancy, France; Inserm CIC, 1433 Epidémiologie clinique, CHRU de Brabois, Nancy, France. RCID: https://orcid.org/0000-0002-9860-7024.

7 – Department of Rheumatology , Centro Hospitalar e Universitário de Coimbra , Coimbra , Portugal ; Coimbra Institute for Clinical and Biomedical Research (iCBR) - Faculty of Medicine , University of Coimbra , Coimbra , Portugal. ORCID: http://orcid.org/0000-0002-2782-6780

8 – Paris Descartes University, Department of Rheumatology, Hôpital Cochin, Assistance Publique - Hôpitaux de Paris, Paris, France; INSERM (U1153): Clinical epidemiology and biostatistics, PRES Sorbonne Paris-Cité, Paris, France. ORCID: https://orcid.org/0000-0003-3009-6229

9 – Sorbonne Université Institut Pierre Louis d'Epidémiologie et de Santé Publique , INSERM , Paris , France ; Department of rheumatology , AP-HP, Pitié Salpêtrière Hospital , Paris , France . ORCID : https://orcid.org/0000-0002-4528-310X

Corresponding Author: Pr. Laure Gossec, Hôpital Pitié-Salpétrière, Service de Rhumatologie, 47-83, boulevard de l'Hôpital - 75013 Paris, France. laure.gossec@aphp.fr

Key words: *rheumatoid arthritis, remission, patient global assessment, quality of life, Predictive Value of Tests, structural damage.*

ABSTRACT

Objectives: To determine if patient global assessment (PGA), as part of Boolean-based definition of remission and individually considered, over the first year of disease course had a significant relationship with structural progression over 3 years in patients with early arthritis (EA).

Methods: Prospective, observational study using ESPOIR cohort data. Remission states were defined as (a) 4v-remission: tender (TJC28), swollen 28-joint counts (SJC28), C-Reactive protein (mg/dl), and PGA (0-10) all ≤1; (b) PGA-near-remission: same parameters with only PGA>1/10; or (c) non-remission. The most favourable definition satisfied both at 6- and 12-months was considered for case-definition. Radiographic progression was determined as the change in total Sharp-van der Heijde score from baseline to 3 years (ΔSHS). The predictive capacities of radiographic damage (ΔSHS≥5 points) of 4v-remission and PGA-near-remission were compared by Odds Ratio (OR). The association between each individual component of remission with ΔSHS was tested through multivariate linear regression analyses, adjusted to baseline radiographic score.

Results: Among 520 patients, 6.7% achieved 4v-remission and 11.9% PGA-near-remission. Radiographic progression (ΔSHS≥5) was observed in 28.6% of patients in 4v-remission (odds ratio versus non-remission, OR=0.32; 95% confidence interval: CI 0.15-0.68) and in 45.2% of patients in PGA-near-remission (OR=0.65; 0.38-1.11). Of the individual components, only SJC28 and CRP were associated with radiographic progression.

Conclusion: All definitions of remission lead to low structural degradation in EA but without statistically significant difference when including or not PGA. Aiming for 4v-remission may not be necessary to prevent radiographic progression, whyle potentially leading to overtreatment.

KEY MESSAGES

- In early arthritis (EA), Boolean 4variable remission is less frequent than PGA-near- remission (only Patient Global Assessment>1/10).
- Radiographic progression (3 years) in EA appeared to similarly decrease in Boolean 4v-remission and in PGA-near-remission.
- PGA-near-remission may be sufficiently stringent to prevent radiographic progression in RA.

INTRODUCTION

Treat-to-target strategies, which include ‘tight control’ approach, aimed at reaching disease remission or, at least, low disease activity,[1] have been widely adopted in the management of rheumatoid arthritis (RA).[2, 3] Achieving and maintaining these targets has been shown to lead to better outcomes for patients.[4, 5] However, important knowledge gaps remain, namely on how to define remission,[6-8] or how strictly to pursue it in practice.[9]

Current remission criteria for RA, endorsed by the American College of Rheumatology (ACR) and by the European League Against Rheumatism (EULAR), include a Boolean-based version based on very low thresholds for 4 variables (or ‘4v-remission’): 0 or 1 swollen 28-joint counts (SJC28), 0 or 1 tender 28-joint counts (TJC28), C-reactive protein (CRP)≤1mg/dL, and patient global assessment (PGA)≤1/10.[10] Several issues with PGA have been raised, including its difficult interpretation and low correlation with disease activity,[11] leading to controversy regarding its inclusion in composite indices.[8, 11, 12] Recent analysis of a large dataset (n>27,700) indicated that the proportion of patients failing remission solely due to PGA>1 (‘PGA-near-remission’) was about double of those attaining 'full' 4v-remission, which means that removing PGA would almost triplicate the remission rate (from 6% to 16%).[13] In that study, despite having no overt signs of inflammation, patients in PGA-near-remission presented levels of disease impact similar to those of patients in non-remission.[14]

However, it remains to be clarified how strong is the association between PGA and key objective outcomes such as radiographic progression.[15] In a prospective observational study of early RA patients (n=527)[16], among the patients in sustained 4v-remission only 31% presented radiographic progression (≥1 unit/year) compared to 45% of those who were in 3v-remission (PGA excluded).[16] The likelihood ratios of good radiographic outcome were not statistically significant for both definitions, despite better results for the 4v-remission.[16] However, because patients in 4v-remission were also included in the 3v-remission status (non-mutually exclusive groups), this study is difficult to interpret.

The definition of target is a key question in clinical practice.[17] Thus, the primary aim of this analysis was to compare the association between achieving 4v-remission and PGA-near-remission during the first year of follow-up, with structural progression over 3 years in patients with early arthritis. We also explored the association of each individual component of the Boolean definition with radiographic damage accrual.

METHODS

Participants and study design

This study used data from patients with early inflammatory arthritis included in the ESPOIR cohort. ESPOIR is an ongoing French multi-centre prospective observational study, which has been previously described.[18] Briefly, patients recruited were 18 to 70 years-old, had two or more peripheral swollen joints for 6 weeks to 6 months, with suspected or confirmed diagnosis of RA, and had not received disease-modifying antirheumatic drugs (DMARDs) or glucocorticoids for longer than 2 weeks before enrolment. Patients received usual care by their rheumatologist, and their follow-up was registered every six months during the first 2 years, then every year.[18]

In the present study, the data analysed pertain to the first 3 years of follow-up; only those patients with all elements needed to calculate ACR/EULAR Boolean-based 4v-remission[10] and radiographic damage progression were included.

Outcome of interest: structural damage

Patients underwent radiography of the hands and wrists and feet at baseline and 3 years. X-Ray films were scored using the Sharp-van der Heijde score (SHS).[19] After computing the change in the SHS ($\Delta SHS_{3y}=SHS_{3y}-SHS_{baseline}$), radiographic damage progression was categorized as $\Delta SHS_{3y} \geq 5$ points (and as $\Delta SHS_{3y} \geq 1$ for sensitivity analyses).

Patient global assessment

PGA was formulated as 'How active do you consider your arthritis?', scored on an 0–100 mm visual analogue scale (VAS), with 'inactive disease' (left, 0) and 'active disease' (right, 100) as anchors.

Remission and PGA-near-remission

The following remission categories were defined: (i) ACR/EULAR Boolean-based remission or 4v-remission (SJC28, TJC28, CRP in mg/dL, and PGA are all ≤1)[10], (ii) PGA-near-remission (only PGA is >1/10), and (iii) non-remission (TJC28 or SJC28 or CRP in mg/dL>1, irrespective of PGA value)[14]. These were mutually exclusive groups. Remission was ascribed as the strictest status at both the 6- and 12-month visits (e.g. a patient in PGA-near-remission at 6 months and in 4v-remission at 12 months was classified as in PGA-near-remission). Putting together 4v-remission and PGA-near-remission leads to a group of patients named as in 3v-remission, which corresponds to the absence of measurable inflammation, whatever the patient assessment.

Other data collected

Age, gender, symptom duration, physical function (Health Assessment Questionnaire - Disability Index, HAQ-DI), fatigue (0-10 VAS), and DMARD treatments were collected for patients' characterization at baseline.

Statistical analysis

The predictive capacities of radiographic damage progression by the different remission definitions (4v-remission, PGA-near-remission and 3v-remission) were compared in several ways: (i) their sensitivity, specificity, positive and negative likelihood ratio (LR+, LR-) were calculated and contrasted; (ii) the odds ratio (OR) and 95% confidence interval (CI) of having structural progression ($\Delta SHS_{3y} \geq 5$ points, primary outcome; ≥1 point, sensitivity analysis) was

compared to non-remission status, (iii) the OR of 4v-remission against PGA-near-remission was also tested in the same way.

To explore the association between each individual component of remission with ΔSHS_{3y}, linear regression analyses were performed, adjusted on baseline SHS, in two steps: (i) firstly, bivariate linear regression was computed taking ΔSHS_{3y} as the dependent variable and mean value of each predictor at 6 and 12 months, in the whole population, (ii) then a multivariate linear regression was made with stepwise selection including the same predictors and outcome. In the sub-group of patients in 3v-remission, the association between PGA and ΔSHS_{3y} was further explored determining the Spearman's correlation coefficient and performing a bivariate linear regression.

There was no imputation of missing data; analyses were performed using the Statistical Analysis System version 9.4.

RESULTS

Patients' characteristics and treatment

In all, 582 (71.5%) of the 813 patients initially registered in the cohort were followed up for 3 years and 520 (64.0%) had all necessary data available and were analysed. Patients' characteristics were typical of early arthritis cohorts (Supplementary Table S1): 76.7% female, mean (standard deviation, SD) age 49.0 (11.9) years, mean duration of symptoms 3.4 (1.7) months. Only 16% of patients used biological DMARDs over the 3 years.

Association between definitions of remission and structural progression

Of the 520 patients, only 35 (6.7%) attained 4v-remission at both 6 and 12 months, while 62 (11.9%) were in PGA-near-remission, resulting in 97 patients (18.6%) attaining 3v-remission. The mean radiographic progression over 3 years was 8.2 SHS units (SD=10.5, median=5.0). The proportion of patients who presented radiographic progression ($\Delta SHS_3 \geq 5$ points) was 28.6% in the 4v-remission group, compared to 45.2% for PGA-near-remission patients (Table

1). The OR versus non-remission was statistically significant (i.e. 95%CI do not include 1) only for the 4v-remission definition (OR =0.32, 95%CI 0.15 to 0.68; OR for PGA-near-remission=0.65, 95%CI 0.38 to 1.11). The direct comparison between patients in 4v and in PGA-near-remission was not statistically significant (OR=0.49, 95%CI 0.20 to 1.18). The odds for radiographic progression for the 3v-remission was also statistically significantly lower than non-remission (OR=0.51; 95%CI 0.32 to 0.80).

As a reminder (Table 1), sensitivity here indicates the probability of radiographic progression in patients in remission (here, very low), and specificity here indicates the probability of no radiographic progression in patients in non-remission (here, very high). However, 4v-remission presented slightly lower sensitivity (12% vs 15%) though slightly higher specificity (96% vs 89%) than PGA-near-remission. The sensitivity analyses with $\Delta SHS_3 \geq 1$ supported similar conclusions (Table 1).

Association between individual components of remission and structural progression

The multivariate analysis by the remission components showed that only SJC28 and CRP were predictive of ΔSHS_{3y}. In this analysis, TJC28 was negatively associated with joint-damage and PGA was dropped from the model (Table 2).

In the 97 patients in 3v-remission, neither Spearman's correlation (r=0.01, p=0.75) nor linear regression (beta=0.015, p=0.74) showed a significant link between PGA and ΔSHS_{3y} (Supplementary Figure S1).

DISCUSSION

This study comparing radiographic damage progression between patients who achieved ACR/EULAR Boolean-based (4v-)remission and patients who fail that target solely due to PGA PGA-near-remission raises interesting perspectives.[10, 16] The percentage of patients achieving PGA-near remission (11.9%) was higher than those achieving full 4v-remission (6.7%). The results indicate that PGA-near-remission at 6 and 12 months is associated with

slightly more frequent structural progression over 3 years than full 4v-remission in early arthritis, both compared with non-remission status. However, when directly comparing radiographic progression in 4v-remission and PGA-near-remission results were not statistically significant. Furthermore, PGA was not a statistically significant predictor of radiographic change in this population, according to multivariate analysis. The strongest drivers of radiographic progression in the present study were SJC28 and CRP. This is in agreement with previous observations.[15]

Comparing the 4v vs the 3v definition of remission reveals that 3v is associated with lower specificity and higher (albeit low) sensitivity.

The implications for practice are not unequivocal. This study confirms the validity of treatment target paradigms in early arthritis, even if the likelihood ratio associated with the stringent definition of remission is still not very strong. Which definition should be favoured? They support the use of the current 4v Boolean-based definition of remission [10] if the intended use prioritizes specificity, i.e. is better served by a definition that is best at assuring structural protection. However, strict adherence to this definition as the target of therapy would expose 11.9% of this population to overtreatment without significant benefit in terms of damage. This latter perspective would favour the 3v-definition of remission.

The inclusion of PGA in both disease activity scores and remission definitions, which have become targets of therapy, reflect the wish to include the patient's perspective in management decisions. However, this should be considered in the light of the evidence above, and elsewhere [13-16] that PGA has a poor relationship with the intensity of the inflammatory process and the structural damage – exactly the main objectives of the therapy being targeted by the definitions.

The small differences observed between PGA-near-remission and full remission may suggest PGA may reflect 'sub-clinical' inflammation. This certainly deserves further investigation. Meanwhile, in practice, patients in PGA-near-remission may be candidates for ultrasound evaluation.

This study has strengths and limitations. The ESPOIR cohort is a French national cohort mirroring clinical practice, with a large number of participants, thus with a good representation of early arthritis patients. One limitation of the present study lies in the fact that remission status were only evaluated at 6 and 12 months, and used.to predict radiographic progression over 3 years. The analyses to support the initial development of the provisional definitions of ACR/EULAR considered remission at 6 OR 12 month data.[10] Although we decided to take into account both 6 AND 12 months data, in the hope that this might reflect more persistent disease control, [5] we did not investigate the stability of the remission status during the second and third year. Another limitation is related to potential lack of power as there were relatively few patients in remission in this cohort. Another issue may be collinearity: PGA is expected to change according to the degree of joint inflammation.[11] To clarify this, we analysed the subgroup of patients in 3v-remission, i.e., for whom visible/measurable inflammation was absent or very low. Finally, it is plausible that different treatments may affect PGA, inflammatory markers and radiographic damage to different degrees. In this case however only 16% of patients were treated with biologics.

In summary, our results suggest that adopting a 3v definition of remission as the target of immunosuppressive therapy in early arthritis, in a clinical practice setting, will probably be associated with a slight increase on the proportion of patients having significant radiographic damage accrual and an important reduction in the number of patients exposed to overtreatment. These observations need to be confirmed in other settings and other definitions of sustained remission deserve consideration. The impact of disease upon patients' lives, will need to be addressed separately, probably through instruments that are discriminative enough to guide its understanding and management.

Acknowledgments

We wish to thank Nathalie Rincheval (EA2415) who performs expert monitoring and data management for ESPOIR, and all the investigators who recruited and followed the patients: F. Berenbaum (Paris-Saint Antoine), MC. Boissier (Paris-Bobigny), A. Cantagrel (Toulouse), P. Fardelonne and P. Boumier (Amiens), RM. Flipo (Lille), Ph. Goupille (Tours), F. Liote (Paris-Lariboisière), O. Vittecoq (Rouen), X. Mariette (Paris-Bicetre), O. Meyer (Paris-Bichat), T. Schaeverbeke (Bordeaux), J. Sibilia (Strasbourg). We wish to thank Gabriel G. Tobon and Valerie Devauchelle-Pensec (Brest), for expert x-ray reading.

Funding: Laure Gossec was partly funded by an Articulum Fellowship. The ESPOIR cohort was created and maintained through an unrestricted grant from Merck Sharp and Dohme (MSD) for the first 5 years. Two additional grants from INSERM were obtained to support part of the biological database. The French Society of Rheumatology, Abbott, Pfizer and Roche-Chugai also supported the ESPOIR cohort study. Ricardo Ferreira was supported by a Grant from ARCo – Associação de Reumatologia de Coimbra, Portugal.

Conflicts of interest:

Ricardo Ferreira has received fees for speaking and/or consulting from Sanofi Genzyme, MSD, and UCB, but these honoraria were unrelated to the present study.

Bruno Fautrel, no conflict of interest to disclose

Alain Saraux has received fees for speaking and/or consulting from AbbVie, BMS, Celgene, Lilly, MSD, Novartis, Pfizer, Roche-Chugai, Sandoz and UCB but these honoraria were unrelated to the present study.

Cécile Gaujoux-Viala has received fees for speaking and/or consulting from Abbvie, Amgen, BMS, Celgene, Gilead, Janssen, Lilly, Medac, MSD, Nordic Pharma, Novartis, Pfizer, Roche, Sandoz, Sanofi, UCB but these honoraria were unrelated to the present study.

Anne-Christine Rat, consulting fees: Lilly, Pfizer, Sanofi-Aventis, all unrelated to the present study.

Francis Guillemin, no conflict of interest to disclose

William Dixon, no conflict of interest to disclose

José A. P. da Silva, has received speaker fees and research grants from several pharmaceutical companies with interests in musculoskeletal diseases. He recognizes no conflict of interest that might be relevant to this study.

Maxime Dougados has received fees for speaking and/or consulting from AbbVie, BMS, Celgene, Janssen, Lilly, MSD, Novartis, Pfizer, Roche-Chugai and UCB but these honoraria were unrelated to the present study.

Laure Gossec: research grants: Pfizer, UCB, Lilly, Bristol-Myers Squibb; consulting fees: AbbVie, Amgen, Biogen, Celgene, Janssen, Lilly, MSD, Nordic Pharma, Novartis, Pfizer, Sanofi-Aventis, UCB; all unrelated to the present study.

REFERENCES

1. Smolen JS, Breedveld FC, Burmester GR, et al. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. Ann Rheum Dis 2015;75:3-15.
2. Singh JA, Saag KG, Bridges SL, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Care Res 2016;68:1-25.
3. Smolen JS, Landewe R, Bijlsma J, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis 2017 Published Online First: 2017/03/08. doi: 10.1136/annrheumdis-2016-210715.
4. Stoffer MA, Schoels MM, Smolen JS, et al. Evidence for treating rheumatoid arthritis to target: results of a systematic literature search update. Ann Rheum Dis 2016;75:16-22.
5. Combe B, Logeart I, Belkacemi MC, et al. Comparison of the long-term outcome for patients with rheumatoid arthritis with persistent moderate disease activity or disease remission during the first year after diagnosis: data from the ESPOIR cohort. Ann Rheum Dis 2015;74:724-9.
6. Porter D, Dale J, Sattar N. How low to aim in rheumatoid arthritis? Learning from other disciplines. Ann Rheum Dis 2014;73:480-2.
7. van Vollenhoven R. Treat-to-target in rheumatoid arthritis — are we there yet? Nature Reviews Rheumatology 2019 Published Online First: doi: 10.1038/s41584-019-0170-5.
8. Pope JE, Michaud K. Is it time to banish composite measures for remission in RA? Arthritis Care Res (Hoboken) 2019 Published Online First: 2019/03/02. doi: 10.1002/acr.23862.
9. Bukhari M. Is remission achievable in most patients with rheumatoid arthritis? Results suggest not. Rheumatology (Oxford) 2019;58:187-8.
10. Felson DT, Smolen JS, Wells G, et al. American College of Rheumatology/European League against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Ann Rheum Dis 2011;70:404-13.
11. Nikiphorou E, Radner H, Chatzidionysiou K, et al. Patient global assessment in measuring disease activity in rheumatoid arthritis: a review of the literature. Arthritis Res Ther 2016;18:251.
12. Ferreira RJO, Duarte C, Ndosi M, et al. The controversy of using PGA to define remission in RA. Nat Rev Rheumatol 2018;14:245.
13. Ferreira RJO, Carvalho PD, Ndosi M, et al. Impact of patient global assessment on achieving remission in patients with rheumatoid arthritis: a multinational study using the METEOR database. Arthritis Care Res (Hoboken) 2019 Published Online First: 2019/03/02. doi: 10.1002/acr.23866.
14. Ferreira RJO, Dougados M, Kirwan J, et al. Drivers of patient global assessment in patients with rheumatoid arthritis who are close to remission: an analysis of 1588 patients Rheumatology (Oxford) 2017 Published Online First: 13 June. doi: 10.1093/rheumatology/kex211.
15. Navarro-Compan V, Gherghe AM, Smolen JS, et al. Relationship between disease activity indices and their individual components and radiographic progression in RA: a systematic literature review. Rheumatology (Oxford) 2015;54:994-1007.
16. Svensson B, Andersson ML, Bala SV, Forslind K, Hafstrom I. Long-term sustained remission in a cohort study of patients with rheumatoid arthritis: choice of remission criteria. BMJ open 2013;3:e003554.
17. Ferreira RJO, Ndosi M, de Wit M, et al. Dual target strategy: a proposal to mitigate the risk of overtreatment and enhance patient satisfaction in rheumatoid arthritis. Ann Rheum Dis. 2018/08/22 ed; 2018.
18. Combe B, Rincheval N. Early lessons from the recent-onset rheumatoid arthritis cohort ESPOIR. Joint Bone Spine 2015;82:13-7.
19. van der Heijde D. How to read radiographs according to the Sharp/van der Heijde method. J Rheumatol 2000;27:261-3.

Table 1. Percentage of patients with radiographic progression for each definition of remission and their predictive capacity measures

Remission status [a]	n (%) of patients with **SHS progression ≥5** points [b]		**OR (95% CI)** [c]	**Accuracy tests**			
	remission	non-remission		Sensitivity	Specificity	LR+ (95% CI)	LR- (95% CI)
4v-remission (n=35) [d]	10/35 (28.6)	236/423 (55.8)	**0.32 (0.15 to 0.68)**	0.12	0.96	2.90 (1.43 to 5.90)	0.92 (0.87 to 0.97)
PGA-near-remission (n=62) [e]	28/62 (45.2)	236/423 (55.8)	0.65 (0.38 to 1.11)	0.15	0.89	1.45 (0.91 to 2.31)	0.95 (0.88 to 1.02)
3v-remission (n=97) [f]	38/97 (39.2)	236/423 (55.8)	**0.51 (0.32 to 0.80)**	0.24	0.86	1.73 (1.20 to 2.50)	0.88 (0.81 to 0.96)
4v-remission vs PGA-Near-remission			0.49 (0.20 to 1.18)				
	SHS progression ≥1 point [b]						
4v-remission (n=35) [d]	22/35 (62.9)	336/423 (79.4)	**0.44 (0.21 to 0.90)**	0.13	0.94	2.12 (1.11 to 4.05)	0.93 (0.86 to 1.00)
PGA-near-remission (n=62) [e]	50/62 (80.6)	336/423 (79.4)	1.08 (0.55 to 2.11)	0.12	0.87	0.94 (0.52 to 1.69)	1.01 (0.93 to 1.10)
3v-remission (n=97) [f]	72/97 (74.2)	336/423 (79.4)	0.75 (0.45 to 1.24)	0.22	0.82	1.26 (0.84 to 1.89)	0.94 (0.85 to 1.05)
4v-remission vs PGA-Near-remission			0.41 (0.16 to 1.03)				

a. Remission was considered if the status was attained at both the 6-month and 12-month time points**.**

b. Radiographic damage progression from baseline to 3 years.

c. In bold are presented the statistically significant differences (i.e. the ones for which the 95%CI do not cross 1.00)

d. SJC28, TJC28, CRP (mg/dL), and PGA all≤1.

e. Same as 4v-remission but PGA>1.

f. SJC28, TJC28, and CRP (mg/dL) all≤1, i.e. PGA not considered. This group equates to the sum of 4v- and 3v-remission.

Legend: SHS - total Sharp-van der Heijde score, LR - Likelihood ratio, CI - Confidence Interval, OR - Odds Ratio.

Table 2. Relationship between 28-joint counts, CRP and PGA with radiographic progression over 3 years [a] (n=520)

Variable [b]	Bivariate linear regression Beta (95% CI), p-value	Multivariate linear regression Beta (95% CI), p-value
SJC28	0.159 (0.150 to 0.777), **0.004**	0.552 (0.203 to 0.901), **0.002**
TJC28	-0.084 (-0.259 to 0.090), 0.344	-0.251 (-0.440 to -0.061), **0.010**
CRP	0.166 (0.071 to 0.260), **0.001**	0.147 (0.051 to 0.243), **0.003**
PGA	0.002 (-0.036 to 0.040), 0.922	ns

a. All analyses were adjusted on baseline SHS, using stepwise model.

b. Each variable is analysed as mean value at the 6 month and 12 month visits

Legend: CI - Confidence Interval, CRP - C-Reactive Protein, n.s. - not statistically significant, PGA - Patient Global Assessment, SJC28 - Swollen 28-joint counts, TJC28 - Tender 28-joint counts

SUPPLEMENTARY MATERIAL

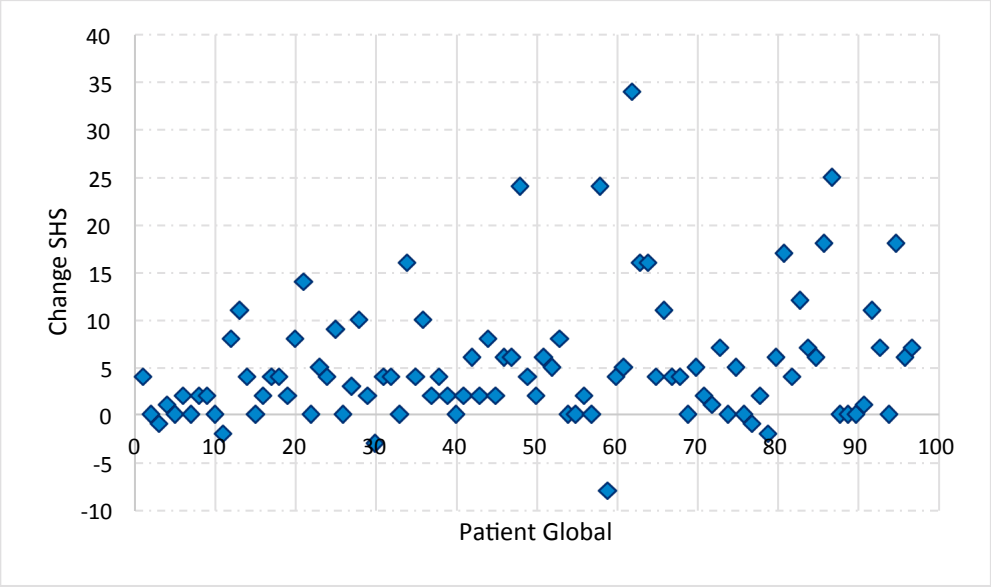
Supplementary Table S1. Patient's characteristics (n=520)

Baseline Characteristics [a]	**value**
Female gender, n (%)	399 (76.7)
Age, years	49.0 (11.9)
Symptom duration, months	3.4 (1.7)
TJC28	8.7 (7.0)
SJC28	7.6 (5.4)
CRP in mg/dL	22.2 (33.1)
PGA (VAS, 0-10)	6.1 (2.5)
HAQ-DI (0-3)	0.97 (0.68)
Fatigue (VAS, 0-10)	4.8 (2.8)
Total SHS	5.4 (7.7)
ACR/EULAR 2010 classification criteria, n (%)	429 (82.5)
ACR 1987 classification criteria, n (%)	318 (61.1)
3-years follow-up characteristics	
Methotrexate use	298 (57.3)
bDMARDs	83 (16.0)
DAS28	2.9 (1.4)
PGA	2.9 (2.6)
HAQ-DI	0.50 (0.57)
Boolean-Remission, n (%)	118 (22.7)

a. Values are mean (standard deviation) unless stated in contrary

Legend: CRP - C-Reactive Protein, HAQ-DI - Health Assessment Questionnaire Disability Index, PGA - Patient Global Assessment, SHS - Sharp van der Heijde radiographic score, SJC28 - Swollen 28-joint counts, TJC28 - Tender 28-joint counts, VAS - visual analogue scale

Supplementary Figure S1. Correlation between PGA (mean values at both 6 and 12 months, 0-100 score) and change in radiographic total SHS scores in 97 patients in 3v-remission.



Manuscript 9

The impact of patient global assessment in the definition of remission as a predictor of long-term radiographic damage in patients with rheumatoid arthritis: protocol for an individual patient data meta-analysis.

Ferreira RJO, Welsing PW, Gossec L, Jacobs JWG, Machado PM
Ndosi M, van der Heijde, da Silva JAP

Acta Reumatol Port. 2018;43(1):52-60.

JOURNAL'S IMPACT FACTOR: 0.776

Number of external citations*: 1

Number of self-citations*: 2

* until 30th august 2019

The impact of patient global assessment in the definition of remission as a predictor of long-term radiographic damage in patients with rheumatoid arthritis: protocol for an individual patient data meta-analysis

Ferreira RJO[1], Welsing PMJ[2], Gossec L[3], Jacobs JWG[2], Machado PM[4], Ndosi M[5], van der Heijde D[6], da Silva JAP[7]

ACTA REUMATOL PORT. 2018;43:52-60

ABSTRACT

Background: Remission is the target for management of rheumatoid arthritis (RA) and intensification of immunosuppressive therapy is recommended for those that do not achieve this status. Patient global assessment (PGA) is the single patient reported outcome considered in the American College of Rheumatology/European League Against Rheumatism remission criteria, but its use as target has been questioned. The primary aim of this study is to assess whether excluding PGA from the definition of disease remission changes the association of disease remission with long-term radiographic damage and physical function in patients with RA.

Methods: Individual patient data meta-analysis using data from randomized controlled trials of biological and targeted synthetic agents, identified through ClinicalTrials.gov and PubMed. Different remission states will be defined: (i) 4v-remission [tender (TJC28) and swollen (SJC28) 28-joint counts both≤1, C-reactive protein (CRP)≤1 (mg/dl), and PGA≤1 (0-10 scale)], (ii) 4v-near-remission (TJC28≤1, SJC28≤1, CRP≤1, and PGA>1), (iii) non-remission (TJC28>1 or SJC28>1 or CRP>1), all mutually exclusive, and (iv) 3v-remission (TJC28≤1, SJC28≤1, CRP≤1). Likelihood ratios will be used to descriptively compare whether meeting the 3v and 4v-remission criteria in a single visit (at 6 or 12 months) predicts good outcome in the second year (1-2y). Differences in the predictive value of PGA in the definition of remission will be assessed by comparing the three mutually exclusive disease states using logistic regression analysis. Good outcome is defined primarily by radiographic damage (no deterioration in radiographic scores, whatever the instrument used in each trial), and secondarily by functional disability (Health Assessment Questionnaire consistently ≤0.5 and no deterioration), and their combination ("overall good outcome"). Additional analyses will consider longer periods over which to (concurrently) define remission status and outcome (between 1-5y and 1-10y), different cut-offs to define good radiographic outcome (change ≤0.5, ≤3 and ≤5 in radiographic score), sustained remission and the influence of treatment and other clinical factors.

Discussion: If 4v-remission and 4v-near-remission are associated with a similar probability of good outcomes, particularly regarding structural damage, the 3v-remission (excluding PGA) could be adopted as the target for immunosuppressive therapy. Patients' perspectives would remain essential, but assessed separately from disease activity, using instruments adequate to guide adjunctive therapies.

Systematic review registration: PROSPERO, CRD42017057099.

Keywords: Rheumatoid arthritis; Outcome research; Patient global assessment; Patient reported outcomes; Disease activity; Remission; Near-remission; Radiographic damage; Function; Individual patient data meta-analysis.

1. Rheumatology Department, Centro Hospitalar e Universitário de Coimbra EPE; UICISA:E, Nursing School of Coimbra
2. Department of Rheumatology & Clinical Immunology, University Medical Center, Utrecht
3. Rheumatology Department, AP-HP, Pitié Salpêtrière Hospital; Sorbonne Université, UPMC Paris 06 University, GRC-UPMC 08
4. Centre for Rheumatology & MRC Centre for Neuromuscular Diseases, University College London
5. Centre for Health and Clinical Research, Department of Nursing and Midwifery, University of the West of England
6. Rheumatology department, Leiden University Medical Centre
7. Coimbra Institute for Clinical and Biomedical Research (iCBR) – Faculty of Medicine – University of Coimbra, Portugal; Rheumatology Department - Centro Hospitalar e Universitário de Coimbra, Portugal

INTRODUCTION

Disease remission or low disease activity is now a realistic therapeutic target in patients with rheumatoid arthritis (RA)[1,2]. The American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) proposed two alternative definitions of remission[3]: one based in Boolean criteria and another on the Simplified Disease Activity Index (SDAI). The Boolean-based definition requires that tender 28-joint count (TJC28), swollen 28-joint count (SJC28), C-Reactive Protein (CRP, in mg/dl), and patient global assessment (PGA, 0–10 scale) are all ≤1. The SDAI criterion requires that the sum of SJC28, TJC28, PGA, CRP and physician/observer global assessment [PhGA] is ≤3.3. These definitions have been recommended for use in daily care of RA[2].

PGA is the sole patient reported outcome (PRO) included in the recommended definitions of remission, having the same weight as other criteria[1-3]. Its inclusion was justified because it represents the patient's perspective and because it proved to discriminate between active and control intervention in clinical trials[3]. However, several studies[4-13] have shown that PGA is not solely influenced by RA disease activity, but also by sociodemographic features, geographic area, and cultural and ethnic aspects, reflecting the fact that PGA scores can be influenced by physical and psychological factors (including disease perception), comorbidities and fibromyalgia, among others[12].

Patients that fail only one of the four Boolean criteria have been called "near-misses"[14] or "near-remission" (designation applied when PGA is the solely criteria >1)[13]. Previous studies[4,13-15] demonstrated that the proportion of near-remission patients could vary from 14.4% up to 38.2%[13], which can represent up to four times the proportion of patients in remission[13]. Following current treatment guidelines[1,2] this state of near-remission would justify intensification of immunosuppressive treatment if based on a shared decision between patient and rheumatologist, taking structural damage, comorbidities or contraindications into account (Overarching Principles A and B)[2].

The importance of incorporating PROs in the overall management plan is indisputable. However, whether PGA conveys information that should be taken into account when considering changing immunosuppressive regimens in patients that have otherwise achieved a remission state based on TJC, SJC and CRP remains unclear. A recent study from our group[12] showed that PGA was weakly correlated with "more" objective disease activity measures (SJC28, TJC28, CRP) but the correlations were strong with pain, fatigue, function, comorbidities, depression and anxiety, and were also significant with other dimensions such as happiness and personality dimensions (weak correlations). Furthermore, it was shown that PGA correlations differ according to disease activity state, with pain, function and joint counts having stronger correlation with PGA when patients are in non-remission.

Immunosuppressive therapy, including biologic disease modifying antirheumatic drugs (bDMARDs), has been shown to improve PGA as disease activity evolves towards remission. However, in cases where PGA is being mainly driven by factors not related to RA, immunosuppressive therapy may not be able to lower PGA ≤1, despite SCJ28, TJC28 and CRP scores ≤1 having already been achieved. From this stage onwards, PGA is not dependent on disease activity and the inability to improve it further should not be interpreted as a failure of the immunosuppressive therapy.

Progression of joint damage is one of the most important outcome measures in RA, because it reflects historic disease activity, is associated with decline of physical function over time, and can be reliably assessed[16]. A recent systematic literature review (SLR)[17] investigated the clinical predictors of radiographic progression in RA, including disease activity indices and their individual components. Regarding the individual components, only SJC and acute phase reactants were associated with radiographic progression. Regarding PGA, the authors concluded that "published data for GH [patient's general health], PGA and EGA [evaluator's global assessment] are limited and do not support their use as unique tools related to progression of joint damage"[17]. The data analysed included two randomized controlled trials (RCTs) and two prospective cohorts, with 1 to 3 years of follow-up, including patients receiving conventional synthetic (cs)DMARDS. However, radiographic progression may be different in patients receiving bDMARDs. A subsequent observational study[18] with 527 patients with early RA, followed for 8 years, demonstrated that 31% of patients reaching remission according to the ACR/EULAR Boolean criteria, at 1, 2, 5, and 8 years (sustained remission) had radiographic progression (>1 unit/ /year). There was no significant contribution of PGA to the prediction of radiographic progression[18].

These observations suggest that the concept of "disease remission" should not include PGA for the

purposes of guiding immunosuppressive therapy. Such a definition of remission, i.e. excluding PGA from ACR/EULAR Boolean definition, might be designated as "remission 3 variables" or "3v-remission". Long-term longitudinal studies, looking at more objective outcomes are required to support this change in the definition of remission.

The primary aim of this study is to assess whether excluding PGA from the definition of disease remission changes the association of disease remission with long-term radiographic damage and physical function in patients with RA.

METHODS/DESIGN

This is an individual patient data (IPD) meta-analysis of published RCTs selected from a systematic literature search.

PROTOCOL AND REGISTRATION

This study protocol was registered in PROSPERO with the number CRD42017057099[19]. The results will be reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Individual Participant Data (PRISMA-IPD), and this checklist (Appendix 1) also served as guidance for writing this protocol.

Ethical approval to this study was granted by the Centro Hospitalar e Universitário de Coimbra Ethics Committee (CHUC-047-17).

ELIGIBILITY CRITERIA

Type of studies

This study will include recently published RCTs, and their long-term extensions (≥ 2 years), which evaluate the efficacy of csDMARDs, bDMARDs or targeted synthetic (ts) DMARD on radiographic damage in patients with RA.

All RCTs assessing radiographic damage assess also physical function as a secondary outcome. Studies with less than two years of follow-up will be excluded.

Participants

Both men and women with diagnosis of RA, and fulfilling the 1987 ACR criteria or the 2010 ACR-EULAR criteria for RA[20,21], will be included.

Types of interventions

Studies testing the efficacy of any bDMARD [Tumor necrosis factor (TNF) inhibitors; Interleukin (IL) inhibitors; B-cell inhibitors; and T-cell inhibitors] or tsDMARD [janus kinase (JAK) inhibitors] will be included. All routes of drug administration will be considered. Studies testing DMARDs dose spacing or suspension will be excluded.

Types of assessments

As a minimum, studies will need to have assessed SJC28, TJC28, CRP, and PGA (in order to determine the Boolean-based criteria) at baseline and at 6 and 12 months and the radiographic damage assessment and physical function at baseline, 12 and 24 months.

IDENTIFYING STUDIES

Studies of interest were searched by one researcher (RF), between November and December of 2016, from the ClinicalTrials.gov registry. The following search strategy was used, without limits: "Rheumatoid arthritis" AND ("radiographic damage" OR "radiographic progression" OR "joint damage"). A second search was also performed in PubMed MEDLINE, for the same time-period, using also the pharmacological names of bDMARDs and tsDMARD as search terms. Additionally, local medical contacts of pharmaceutical companies were approached in order to identify possible published studies missed in previous searches and how to get access to their IPD. A summary table with the results of this search is presented in Appendix 2.

STUDY SELECTION PROCESS

Full papers of the identified studies were obtained and checked against the inclusion criteria by two researchers (RF and JAPS) independently.

DATA COLLECTION PROCESSES

Not all published studies have IPD available, which can be the case if patients did not give permission for broader research than the original study. The timing of data availability after study publication may also vary according to data holder policy[22]: while some companies make the data available immediately after the first publication, others only do it after the investigational product has been approved for use in both the United States and European Union. Thus, after study selection (Appendix 2) a research proposal was submitted to all sponsors of those trials, asking for IPD access.

DATA ITEMS

In addition to the radiographic damage score and

physical function (outcomes), and to SJC28, TJC28, CRP, and PGA (for remission definition) the following variables will be extracted from the trials: (i) patient characteristics – gender, age at baseline; (ii) clinical characteristics – disease duration at baseline, rheumatoid factor (RF) status, anti-citrullinated peptide antibody (ACPA) status, and treatment arm (iii) trial/visit information variables, namely anonymised patient identification (ID) code, visit number or sequence, and visit date. Appendix 3 provides a list off all essential variables that will be extracted from each trial.

IPD INTEGRITY

Any important issues identified when checking IPD, such as data plausibility, consistency, completeness or baseline imbalance will be reported and summarised using a PRISMA-IPD flow diagram.

RISK OF BIAS ASSESSMENT OF INDIVIDUAL STUDIES

The quality and potential bias of included studies will be assessed using the guidelines for assessing quality in prognostic studies, assigning an overall quality score per study of between 0 and 6 points according to Hayden *et al.*[23] The six topics assessed are: study participation, study attrition, prognostic factor measurement, outcome measurement, confounding measurement and account, and analysis. Of particular relevance for this study will be the assessment of radiographic damage. A list of ten possible biases in the assessment of radiographic data was described by van der Heijde[24] and this information will be collected separately for quality assessment of the radiographic outcome, but will not be used as the basis for including/excluding studies.

SPECIFICATION OF OUTCOMES AND EFFECT MEASURES

For the purposes of this study the methodology adopted by the ACR/EULAR group[3] to define good outcome in radiographic damage and function (separately and combined) will be adopted. Using the same definitions will allow direct comparisons of the results/conclusion. However, in the present study different definitions of "good radiographic outcome" will be evaluated (for more details please see "Exploration in variation effects (sensitivity analyses)" section).

Primary outcome:

a) Percentage of individuals with a good radiographic outcome during the second year of the trial (i.e. between month 12 and month 24).

"Good radiographic outcome" is defined as stable radiographic scores (change ≤0 in Sharp[25] or modified Sharp scores[26-28] during the second year of the trial).

Secondary outcomes:

b) Percentage of individuals with a good functional outcome during the second year of the trial.

"Good physical function outcome" is defined as stable and low scores of Health Assessment Questionnaire (HAQ)[29] (change ≤0 and HAQ score consistently ≤0.5 during the second year of the trial).

c) Percentage of individuals with overall good outcome during the second year of the trial.

"Overall good outcome" is considered the combination of "good radiographic outcome" and "good physical function outcome".

Additional secondary outcomes:

The above-mentioned outcomes assessed the stability between 1 and 2 years. Additional secondary outcomes will assess stability between 1 and 5 years and between 1 and 10 years after baseline for a), b) and c), in trials with such long follow-up.

Measures of association:

The principal effect measure for all outcomes will be the positive (LR+) and negative likelihood ratios (LR-).

COMPARISONS: DEFINITIONS OF REMISSION

Analyses will be based on the definition of different remission states (Figure 1), assessed at 6 months and 12 months, following the methodology adopted by the ACR/EULAR committee[3], as follows:

a) ACR/EULAR Boolean-based remission[3], also designed in this project as "4v-Remission" (i.e., TJC28≤1, SJC28≤1, CRP mg/dl ≤1, and PGA≤1/10)
b) "4v-near-remission"[13,14], defined as TJC28≤1, SJC28≤1, CRP mg/dl ≤1, and PGA>1.
c) "Non-remission" defined as TJC28>1 or SJC28>1 or CRP mg/dl >1.

The above three definitions are mutually exclusive, i.e. each patient will be categorized in one group only.

d) "3v-remission" defined as TJC28≤1, SJC28≤1, CRP mg/dl ≤1.

All remission definitions are considered to be satisfied when they are satisfied either at 6 or 12 months follow-up.

The LR for good outcome associated with 4v and 3v--remission states will be descriptively compared. Then,

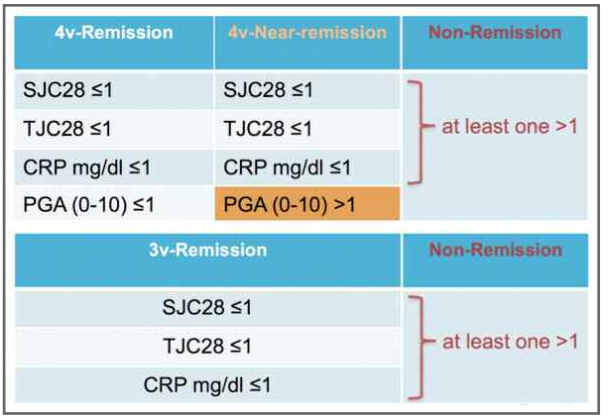


FIGURE 1. Definitions of Boolean remission considered for this study, adapted from the ACR/EULAR Boolean definition

CRP: C-reactive protein, PGA: patient global assessment; SJC28: swollen 28-joint counts; TJC28: tender 28-joint counts

an analysis will be performed for evaluating the (lack of) additional predictive value of PGA in the definition of remission, using the mutually exclusive categories ("4v-remission", "4v-near-remission" and "non-remission") (for more details please see "data analyses" section and Appendix 4).

DEFINITIONS OF SUSTAINED REMISSION

Sensitivity analyses will assess the influence of sustained remission, i.e. remission in more than a single time-point (6 or 12 months), in the prediction of good outcomes in RA. Because there is no currently uniform definition of sustained remission, the following will be tested: (i) remission at 6 and 12 months, (ii) remission at two consecutive visits among all time-points consistently available during the first year in all trials, ideally separated by 3 months (i.e. 3, 6, 9, and 12 months), as suggested by Konijn *et al.*[30], (iii) having or not ≥50% of visits in remission, and (iv) using the "Continuity Reward" (ConRew) score proposed by Boers *et al.*[31], which gives 1 point for a period in remission and a bonus (1 point more) if the subsequent period is also remission or if it is the last observation period. Because ConRew is a continuous score and the distributions are expected to be strongly right skewed[31], the 25th percentile will be considered as cut-off to dichotomize sustained versus non-sustained remission. Definitions (iii) and (iv) will consider the visits from the beginning to the end of the follow-up under consideration, i.e. not only the first year of the trial and patients will be classified to the 'highest category' for definitions ii and iv, e.g. when they satisfy both the 4v-remission and 4v--near-remission definitions at two consecutive visits, or have both a ConRew score >25th percentile based on 4v-remission and 4v-near remission, they are assigned to the 4v-remission category.

DATA ANALYSIS AND SYNTHESIS

Data analysis

To guarantee privacy and security of IPD, the platforms in which the data is available require that statistics be performed via remote and secure online platforms, which impedes data download. All platforms commonly allow the use of SAS software, which will be used within each platform. For data synthesis, Stata software version 14 will be used. Thus, the same procedures will need to be performed in each platform.

Means and standard deviations (SD) will be used to describe normally distributed continuous data, medians and interquartile ranges to describe continuous data that are not normally distributed, and frequencies and percentages will be used for categorical data. Data will be described using 95% confidence intervals (95% CI).

The number of true positive (TP), true negative (TN), false negative (FN) and false positive (FP) statistics will be extracted for each dataset. Then, sensitivity, specificity, positive and negative predictive value (PPV and NPV) will be determined for being in (sustained) remission (by 3v and 4v-remission) to predict good radiographic outcome at 2-years after baseline. The LR+ and LR- will then be calculated by the formulas: *sensitivity*/(*1-specificity*) and (1-*sensitivity*)/*specificity*, respectively. All analyses will be repeated for secondary outcomes: good function, and overall good outcome.

LRs, calculated as above, will be descriptively compared. In a second phase, participants in non-remission will be excluded from analyses and LRs for good radiographic outcome will be calculated for "4v-remission" versus "4v-near-remission", as a means to assess the predictive impact of PGA (Appendix 4, image C).

To additionally test the predictive value of PGA in the definition of remission, logistic regression will be used with the outcome of interest - radiographic stability - as dependent variable. The independent variables will include remission (a categorical variable indicating whether a patient is in "4v-remission", "4v-near-remission", or not satisfying any of these definitions, i.e. "non-remission") (Appendix 4, images D and E). The regression coefficient/odds ratio (OR) (and 95% CI) comparing the "4v-near-remission" category

with the "4v-remission" category will indicate whether there is any relevant difference between these groups and, thus, whether PGA has any additional predictive value for outcome.

Missing data will not be submitted to any method of data imputation, based on the comparable results of imputed and non-imputed data shown by a similar analysis[30]. The number and percentage of patients with missing values for each variable will be reported per trial.

Measures to adjust for confounders

In order to adjust for important covariates (gender, age at baseline, disease duration at baseline, RF, ACPA, radiographic damage at baseline, treatment arm), logistic regression (as above) will be used in individual studies.

Data synthesis

A two-step approach will be followed in this IPD meta-analysis. Thus, the TP, TN, FN, and FP results obtained for each trial in a first step (described above) will be used to synthetize the data in a second step. To consider the results from the mutually exclusive definitions of remission and to take into account the influence of the covariates, the OR and its standard error (SE) resulting from the logistic regression will also be synthesized, using appropriate fixed-effect and random-effects approaches, as suggested by Chang and Hoaglin[32].

As the definitions of remission will be the same over all studies as well as the definition of the outcome (as they are calculated by the authors), a Bivariate hierarchical model with random effect will be used to summarize the diagnostic association measure[33].

The I^2 of Higgins and Thompson will be calculated to quantify heterogeneity[34,35].

EXPLORATION IN VARIATION EFFECTS (SENSITIVITY ANALYSES)

In recent years a statistically significant reduction in radiographic progression during clinical studies in patients with RA has become difficult to detect due to early-escape study designs and to declining rates of progression in control-group patients[36]. For this reason, and also to be consistent with the methodology used by ACR and EULAR to establish the current definition of remission, a strict definition of good outcome was adopted for this study, i.e, a change ≤0 in radiographic progression. However, the majority of recent studies consider a cut-off ≤0.5 to define radiographic stability, to allow for a maximum change of 1 unit by one of the two readers. Therefore, a sensitivity analysis will consider change ≤0.5 units as cut-off for radiographic damage progression. Also, in order to account for inter and intra-rater variation of the radiographic score[30,37,38] and to provide information on the magnitude of structural damage, two additional cut-offs to define good radiographic outcome will be considered: ≤3 and ≤5 units of the radiographic score. It is also argued that the number of years of follow-up could affect the results of radiographic outcomes[18]. Thus, in addition to the main analysis of the 2-year outcome (the most frequently reported), outcomes at 5 and 10 years after baseline will also be assessed, i.e, 4 and 9 years' stability after 12 months.

The definition of "sustained" remission (and non-remission) based on only 1 time point or even 2 consecutive time points may not fully capture all relevant information[31]. Thus we will explore whether multiple remission and relapse periods are related to long-term radiographic progression and compare the performance of 3v and 4v-remission definitions, namely using the ConRew score[31], as explained above.

We will, finally, evaluate whether the relationship between the definition of remission and outcome is affected by treatment (mono versus combined), disease duration (early versus established), and history of previous DMARD treatments (naive versus failure/non-responders).

DISCUSSION

This study will evaluate whether the predictive value of 3v and 4v-remission states regarding the development of structural damage are comparable. If confirmed, the inclusion of PGA in the definition of remission as treatment target should be revised (to 3v-remission), thus helping to avoid unnecessary immunosuppressive treatment escalation and associated risks. Given that more patients attain 3v than 4v-remission, it is expected that the value (long term benefit) of available therapies will be reassessed and probably recognized as higher than previously acknowledged.

If no relevant difference is observed by including or excluding PGA from the definition, the proposal towards the adoption of two separate targets for the treatment of RA (control of the disease process and control of its impact upon the patient's life) will be strongly supported. Disease impact will continue to be core to the assessment and management of the disease but it will be better served by instruments that allow the

health professionals to understand the reasons driving a high-perceived impact of the disease. Once disease control is achieved, adjunctive pharmacological and non-pharmacological therapies of different nature may be considered, based on the understanding of disease impact in the individual patient[12,13].

In case the results demonstrate that including PGA in the ACR/EULAR Boolean-based definition increases its predictive value of good outcomes, the current definition of remission is supported. This would not invalidate the need to consider a separate patient impact target[39,40]. We would argue, in any case, following available evidence, that the formulation of PGA should be standardized[41,42] and that patients should have a dedicated debriefing about this measure in order to improve its reliability[43].

An IPD meta-analysis is adequate for this study because it allows calculating a new definition of remission in RA: the 3v-remission, which includes the same variables used to assess remission by current definitions. Being "new", this definition has never been published, thus not accessible through a conventional meta-analysis.

This type of meta-analysis has many advantages but also some limitations[44-46]. The main advantages of this specific study include access: (i) to large datasets of patients, (ii) with long-term outcome assessment, and (iii) rigorous data collection. The potential limitations are mainly related with the different designs of the RCTs included, namely: different inclusion criteria (e.g. patients naive versus non-responders to MTX), different treatments (e.g. patient in mono versus combined DMARD therapy), different time point assessments within the same period, or variation in radiographic scoring. To face these limitations different sub-group and sensitivity analyses are planned, that will allow guaranteeing the rigor and generalizability of the results. The inclusion of highly experienced experts in radiographic outcome assessment and in RCT design, development, and statistical analyses in this international consortium of researchers will also contribute to overcome possible difficulties. All the authors will be engaged in close critical appraisal in every step of the analyses to ensure the validity of the results and conclusions of this study. To guarantee quality control and reproducibility of the procedures the analysis's syntax will be recorded.

Two important decisions that were taken during study design are important to highlight. The first decision was regarding the number of studies to include. Usually, turning large amounts of data into actionable information allows better contributions in epidemiology[47]. The authors agreed that there was no need to include all existing RCTs testing biological and targeted synthetic agents, but including data from different data-holders would strengthen this study. The second decision was related with the fact that this study is questioning the current ACR/EULAR Boolean-based definition of remission and how strictly should this study reproduce their methodological decisions. It was decided to reproduce their analysis but performing further sensitivity analysis using other methodological options. An example was the additional cut-off for the definition of good radiographic outcomes. Another example was the definition of sustained remission: although ACR/EULAR committee[3] have used a single point in time (6 or 12 months) to define remission and despite the nonexistence of a uniform definition of sustained remission[30], this study will also use four additional definitions.

The present study considers radiographic score as primary endpoints and function (HAQ) and overall outcomes as secondary endpoints. This decision was based on the fact that HAQ: (i) is not only an outcome measure (cumulative functional deterioration over time) but also a disease activity-related measure (impact of current disease activity on function a specific point in time)[48], and (ii) is subjective[49,50], i.e. does not measure functioning of patients, but assesses their opinion on their functioning. So, the factors underlying an unjustifiably high PGA would be expected to have a similar effect upon HAQ, confounding the argument.

At the time of submission of this manuscript, all the five pharmaceutical companies (MSD/JANSSEN, Pfizer, Abbvie, Roche and UCB) contacted had already granted us access to their RCTs, which demonstrates the perceived value of this research project. These positive answers also assure that structural damage and functional outcomes after 5 and 10-years of DMARD initiation will also be possible to be compared.

ACKNOWLEDGMENTS

We wish to thank Cátia Duarte and Eduardo Santos (Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal) for critically revising the manuscripts for its intellectual content.

CORRESPONDENCE TO

José António Pereira da Silva
Centro Hospitalar Universitário de Coimbra, EPE.
Serviço de Reumatologia, Piso 7.
Praceta Professor Mota Pinto
3000-075 Coimbra. Portugal
E-mail: jdasilva@ci.uc.pt

REFERENCES

1. Smolen JS, Breedveld FC, Burmester GR, et al. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. Ann Rheum Dis 2015; 75: 3-15.
2. Smolen JS, Landewe R, Bijlsma J, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis 2017; 76: 960-977.
3. Felson DT, Smolen JS, Wells G, et al. American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Arthritis Rheum 2011; 63: 573-586.
4. Vermeer M, Kuper HH, van der Bijl AE, et al. The provisional ACR/EULAR definition of remission in RA: a comment on the patient global assessment criterion. Rheumatology (Oxford) 2012; 51: 1076-1080.
5. Khan NA, Spencer HJ, Abda E, et al. Determinants of discordance in patients' and physicians' rating of rheumatoid arthritis disease activity. Arthritis Care Res (Hoboken) 2012; 64: 206--214.
6. Ward MM, Guthrie LC, Alba MI. Measures of arthritis activity associated with patient-reported improvement in rheumatoid arthritis when assessed prospectively versus retrospectively. Arthritis Care Res (Hoboken) 2015; 67: 776-781.
7. Egsmose EL, Madsen OR. Interplay between patient global assessment, pain, and fatigue and influence of other clinical disease activity measures in patients with active rheumatoid arthritis. Clin Rheumatol 2015; 34: 1187-1194.
8. Sokka T, Kautiainen H, Pincus T, et al. Disparities in rheumatoid arthritis disease activity according to gross domestic product in 25 countries in the QUEST-RA database. Ann Rheum Dis 2009; 68: 1666-1672.
9. Masri KR, Shaver TS, Shahouri SH, et al. Validity and reliability problems with patient global as a component of the ACR/EULAR remission criteria as used in clinical practice. J Rheumatol 2012; 39: 1139-1145.
10. Studenic P, Radner H, Smolen JS, Aletaha D. Discrepancies between patients and physicians in their perceptions of rheumatoid arthritis disease activity. Arthritis Rheum 2012; 64: 2814--2823.
11. Inanc N, Yilmaz-Oner S, Can M, Sokka T, Direskeneli H. The role of depression, anxiety, fatigue, and fibromyalgia on the evaluation of the remission status in patients with rheumatoid arthritis. J Rheumatol 2014; 41: 1755-1760.
12. Ferreira RJO, Duarte C, Ndosi M, de Wit M, Gossec L, da Silva JAP. Suppressing inflammation in rheumatoid arthritis: Does patient global assessment blur the target? A practice–based 2018; 70(3):369-378.
13. Ferreira RJO, Dougados M, Kirwan J, et al. Drivers of patient global assessment in patients with rheumatoid arthritis who are close to remission: an analysis of 1588 patients. Rheumatology (Oxford) 2017; 56: 1573-1578.
14. Studenic P, Smolen JS, Aletaha D. Near misses of ACR/EULAR criteria for remission: effects of patient global assessment in Boolean and index-based definitions. Ann Rheum Dis 2012; 71: 1702-1705.
15. Balogh E, Dias JM, Orr C, et al. Comparison of remission criteria in a tumour necrosis factor inhibitor treated rheumatoid arthritis longitudinal cohort: patient global health is a confounder. Arthritis Res Ther 2013; 15: R221.
16. Landewe R, van de Heijde D. Is radiographic progression a realistic outcome measure in clinical trials with early inflammatory arthritis? Clin Exp Rheumatol 2003; 21: S37-41.
17. Navarro-Compan V, Gherghe AM, Smolen JS, Aletaha D, Landewe R, van der Heijde D. Relationship between disease activity indices and their individual components and radiographic progression in RA: a systematic literature review. Rheumatology (Oxford) 2015; 54: 994-1007.
18. Svensson B, Andersson ML, Bala SV, Forslind K, Hafstrom I. Long-term sustained remission in a cohort study of patients with rheumatoid arthritis: choice of remission criteria. BMJ open 2013; 3: e003554.
19. Ferreira RJO, Machado PM, Gossec L, et al. Long-term predictive value of including patient global assessment in Boolean remission regarding radiographic damage and physical function in patients with rheumatoid arthritis: protocol for an individual patient data meta-analysis PROSPERO2017 http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017057099. Accessed in October 25th 2017.
20. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988; 31: 315--324.
21. Aletaha D, Neogi T, Silman AJ, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2010; 69: 1580-1588.
22. Committee on Strategies for Responsible Sharing of Clinical Trial; Data Board on Health Sciences Policy; Institute of Medicine. Discussion Framework for Clinical Trial Data Sharing: Guiding Principles, Elements, and Activities. Washington (DC): National Academies Press (US); 2014.
23. Hayden JA, Cote P, Bombardier C. Evaluation of the quality of prognosis studies in systematic reviews. Ann Intern Med 2006; 144: 427-437.
24. van der Heijde D. Structural damage in rheumatoid arthritis as visualized through radiographs. Arthritis Res 2002; 4 Suppl 2: S29-33.
25. Sharp JT, Lidsky MD, Collins LC, Moreland J. Methods of scoring the progression of radiologic changes in rheumatoid arthritis. Correlation of radiologic, clinical and laboratory abnormalities. Arthritis Rheum 1971; 14: 706-720.
26. Ory PA. Interpreting radiographic data in rheumatoid arthritis. Ann Rheum Dis 2003; 62: 597-604.
27. van der Heijde D. How to read radiographs according to the Sharp/van der Heijde method. J Rheumatol 2000; 27: 261-263.
28. van der Heijde DM, van Riel PL, Nuver-Zwart IH, Gribnau FW, vad de Putte LB. Effects of hydroxychloroquine and sulphasalazine on progression of joint damage in rheumatoid arthritis. Lancet 1989; 1: 1036-1038.
29. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum 1980; 23: 137-145.
30. Konijn NPC, van Tuyl LHD, Boers M, et al. Do Short and Sustained Periods of American College of Rheumatology/European League Against Rheumatism Remission Predict Functional and Radiographic Outcome in Early Rheumatoid Arthritis Patients With Low Overall Damage Progression? Arthritis Care Res (Hoboken) 2017; 69: 989-996.
31. Boers M, Berkhof J, Twisk JW, et al. A new graph and scoring system simplified analysis of changing states: disease remissions in a rheumatoid arthritis clinical trial. J Clin Epidemiol 2010; 63: 633-637.

32. Chang BH, Hoaglin DC. Meta-Analysis of Odds Ratios: Current Good Practices. Med Care 2017; 55: 328-335.
33. Macaskill P, Gatsonis C, Deeks JJ, Harbord RM, Takwoingi Y. Chapter 10 Analysing and Presenting Results. In: Deeks JJ, Bossuyt PM, Gatsonis C, editors. Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy Version 10: The Cochrane Collaboration, 2010. http://srdta.cochrane.org/ Accessed in October 25th 2017.
34. Moayyedi P. Meta-analysis: Can we mix apples and oranges? Am J Gastroenterol 2004; 99: 2297-2301.
35. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta--analysis. Stat Med 2002; 21: 1539-1558.
36. Landewe RB, Connell CA, Bradley JD, et al. Is radiographic progression in modern rheumatoid arthritis trials still a robust outcome? Experience from tofacitinib clinical trials. Arthritis Res Ther 2016; 18: 212.
37. van der Heijde D, Tanaka Y, Fleischmann R, et al. Tofacitinib (CP-690,550) in patients with rheumatoid arthritis receiving methotrexate: twelve-month data from a twenty-four-month phase III randomized radiographic study. Arthritis Rheum 2013; 65: 559-570.
38. Fleischmann RM, Huizinga TW, Kavanaugh AF, et al. Efficacy of tofacitinib monotherapy in methotrexate-naive patients with early or established rheumatoid arthritis. RMD open 2016; 2: e000262.
39. van Tuyl LHD, Boers M. Rheumatoid arthritis: Remission - keeping the patient experience front and centre. Nat Rev Rheumatol 2017; 13: 573-574.
40. Ferreira RJO, Duarte C, Ndosi M, de Wit M, Gossec L, da Silva JAP. The controversy of using PGA to define remission in RA. Nat Rev Rheumatol 2018; 14: 245.
41. Nikiphorou E, Radner H, Chatzidionysiou K, et al. Patient global assessment in measuring disease activity in rheumatoid arthritis: a review of the literature. Arthritis Res Ther 2016; 18: 251.
42. Ferreira RJO, Eugenio G, Ndosi M, Silva C, Medeiros C, Duarte C, da Silva JAP. Influence of the different "patient global assessment" formulations on disease activity score by different indices in rheumatoid arthritis. Clin Rheumatol. Online First: 10 March 2018. doi:10.1007/s10067-018-4063-9
43. Henriques M, Duarte C, Ndosi M, Marques A, Silva da Silva JAP, Ferreira RJO. "It can't be zero": a qualitative study of patients' perspective on patient global assessment in rheumatoid arthritis [abstract]. Ann Rheum Dis 2017; 76(Suppl 2): 112-112.
44. Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data: rationale, conduct, and reporting. BMJ 2010; 340: c221.
45. Stewart LA, Tierney JF. To IPD or not to IPD? Advantages and disadvantages of systematic reviews using individual patient data. Eval Health Prof 2002; 25: 76-97.
46. Stewart LA, Tierney JF. Reviews of individual patient data. 2011. In: Cochrane Handbook for Systematic Reviews of Interventions. Chichester: John Wiley & Sons Ltd.
47. European Commission. Directorate-General for Health and Consumers. Unit D3 eHealth and Health Technology Assessment. The Use of Big Data in Public Health Policy and Research: Background information document. Brussels, 2014.
48. Welsing PM, van Gestel AM, Swinkels HL, Kiemeney LA, van Riel PL. The relationship between disease activity, joint destruction, and functional capacity over the course of rheumatoid arthritis. Arthritis Rheum 2001; 44: 2009-2017.
49. Wolfe F. A reappraisal of HAQ disability in rheumatoid arthritis. Arthritis Rheum 2000; 43: 2751-2761.
50. van den Ende CH, Hazes JM, Le Cessie S, Breedveld FC, Dijkmans BA. Discordance between objective and subjective assessment of functional ability of patients with rheumatoid arthritis. Br J Rheumatol 1995; 34: 951-955.

PRISMA-IPD CHECKLIST OF ITEMS TO INCLUDE WHEN REPORTING A SYSTEMATIC REVIEW AND META-ANALYSIS OF INDIVIDUAL PARTICIPANT DATA (IPD)

PRISMA-IPD Section/topic	Item No	Checklist item	Reported on page
Title			
Title	1	Identify the report as a systematic review and meta-analysis of individual participant data.	
Abstract			
Structured summary	2	Provide a structured summary including as applicable:	
		Background: state research question and main objectives, with information on participants, interventions, comparators and outcomes.	
		Methods: report eligibility criteria; data sources including dates of last bibliographic search or elicitation, noting that IPD were sought; methods of assessing risk of bias.	
		Results: provide number and type of studies and participants identified and number (%) obtained; summary effect estimates for main outcomes (benefits and harms) with confidence intervals and measures of statistical heterogeneity. Describe the direction and size of summary effects in terms meaningful to those who would put findings into practice.	
		Discussion: state main strengths and limitations of the evidence, general interpretation of the results and any important implications.	
		Other: report primary funding source, registration number and registry name for the systematic review and IPD meta-analysis.	
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of the questions being addressed with reference, as applicable, to participants, interventions, comparisons, outcomes and study design (PICOS). Include any hypotheses that relate to particular types of participant-level subgroups.	
Methods			
Protocol and registration	5	Indicate if a protocol exists and where it can be accessed. If available, provide registration information including registration number and registry name. Provide publication details, if applicable.	
Eligibility criteria	6	Specify inclusion and exclusion criteria including those relating to participants, interventions, comparisons, outcomes, study design and characteristics (e.g. years when conducted, required minimum follow-up). Note whether these were applied at the study or individual level i.e. whether eligible participants were included (and ineligible participants excluded) from a study that included a wider population than specified by the review inclusion criteria. The rationale for criteria should be stated.	
Identifying studies – information sources	7	Describe all methods of identifying published and unpublished studies including, as applicable: which bibliographic databases were searched with dates of coverage; details of any hand searching including of conference proceedings; use of study registers and agency or company databases; contact with the original research team and experts in the field; open adverts and surveys. Give the date of last search or elicitation.	

continues on the next page

CONTINUATION

PRISMA-IPD Section/topic	Item No	Checklist item	Reported on page
Identifying studies – search	8	Present the full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection processes	9	State the process for determining which studies were eligible for inclusion.	
Data collection processes	10	Describe how IPD were requested, collected and managed, including any processes for querying and confirming data with investigators. If IPD were not sought from any eligible study, the reason for this should be stated (for each such study).	
		If applicable, describe how any studies for which IPD were not available were dealt with. This should include whether, how and what aggregate data were sought or extracted from study reports and publications (such as extracting data independently in duplicate) and any processes for obtaining and confirming these data with investigators.	
Data items	11	Describe how the information and variables to be collected were chosen. List and define all study level and participant level data that were sought, including baseline and follow-up information. If applicable, describe methods of standardising or translating variables within the IPD datasets to ensure common scales or measurements across studies.	
IPD integrity	A1	Describe what aspects of IPD were subject to data checking (such as sequence generation, data consistency and completeness, baseline imbalance) and how this was done.	
Risk of bias assessment in individual studies.	12	Describe methods used to assess risk of bias in the individual studies and whether this was applied separately for each outcome. If applicable, describe how findings of IPD checking were used to inform the assessment. Report if and how risk of bias assessment was used in any data synthesis.	
Specification of outcomes and effect measures	13	State all treatment comparisons of interests. State all outcomes addressed and define them in detail. State whether they were pre-specified for the review and, if applicable, whether they were primary/main or secondary/additional outcomes. Give the principal measures of effect (such as risk ratio, hazard ratio, difference in means) used for each outcome.	
Synthesis methods	14	Describe the meta-analysis methods used to synthesise IPD. Specify any statistical methods and models used. Issues should include (but are not restricted to):	
		• Use of a one-stage or two-stage approach.	
		• How effect estimates were generated separately within each study and combined across studies (where applicable).	
		• Specification of one-stage models (where applicable) including how clustering of patients within studies was accounted for.	
		• Use of fixed or random effects models and any other model assumptions, such as proportional hazards.	
		• How (summary) survival curves were generated (where applicable).	
		• Methods for quantifying statistical heterogeneity (such as I2 and $\tau 2$).	
		• How studies providing IPD and not providing IPD were analysed together (where applicable).	
		• How missing data within the IPD were dealt with (where applicable).	

continues on the next page

CONTINUATION

PRISMA-IPD Section/topic	Item No	Checklist item	Reported on page
Exploration of variation in effects	A2	If applicable, describe any methods used to explore variation in effects by study or participant level characteristics (such as estimation of interactions between effect and covariates). State all participant-level characteristics that were analysed as potential effect modifiers, and whether these were pre-specified.	
Risk of bias across studies	15	Specify any assessment of risk of bias relating to the accumulated body of evidence, including any pertaining to not obtaining IPD for particular studies, outcomes or other variables.	
Additional analyses	16	Describe methods of any additional analyses, including sensitivity analyses. State which of these were pre-specified.	
Results			
Study selection and IPD obtained	17	Give numbers of studies screened, assessed for eligibility, and included in the systematic review with reasons for exclusions at each stage. Indicate the number of studies and participants for which IPD were sought and for which IPD were obtained. For those studies where IPD were not available, give the numbers of studies and participants for which aggregate data were available. Report reasons for non-availability of IPD. Include a flow diagram.	
Study characteristics	18	For each study, present information on key study and participant characteristics (such as description of interventions, numbers of participants, demographic data, unavailability of outcomes, funding source, and if applicable duration of follow-up). Provide (main) citations for each study. Where applicable, also report similar study characteristics for any studies not providing IPD.	
IPD integrity	A3	Report any important issues identified in checking IPD or state that there were none.	
Risk of bias within studies	19	Present data on risk of bias assessments. If applicable, describe whether data checking led to the up-weighting or down-weighting of these assessments. Consider how any potential bias impacts on the robustness of meta-analysis conclusions.	
Results of individual studies	20	For each comparison and for each main outcome (benefit or harm), for each individual study report the number of eligible participants for which data were obtained and show simple summary data for each intervention group (including, where applicable, the number of events), effect estimates and confidence intervals. These may be tabulated or included on a forest plot.	
Results of syntheses	21	Present summary effects for each meta-analysis undertaken, including confidence intervals and measures of statistical heterogeneity. State whether the analysis was pre-specified, and report the numbers of studies and participants and, where applicable, the number of events on which it is based.	
		When exploring variation in effects due to patient or study characteristics, present summary interaction estimates for each characteristic examined, including confidence intervals and measures of statistical heterogeneity. State whether the analysis was pre-specified. State whether any interaction is consistent across trials.	
		Provide a description of the direction and size of effect in terms meaningful to those who would put findings into practice.	
Risk of bias across studies	22	Present results of any assessment of risk of bias relating to the accumulated body of evidence, including any pertaining to the availability and representativeness of available studies, outcomes or other variables.	

continues on the next page

CONTINUATION

PRISMA-IPD Section/topic	Item No	Checklist item	Reported on page
Additional analyses	23	Give results of any additional analyses (e.g. sensitivity analyses). If applicable, this should also include any analyses that incorporate aggregate data for studies that do not have IPD. If applicable, summarise the main meta-analysis results following the inclusion or exclusion of studies for which IPD were not available.	
Discussion			
Summary of evidence	24	Summarise the main findings, including the strength of evidence for each main outcome.	
Strengths and limitations	25	Discuss any important strengths and limitations of the evidence including the benefits of access to IPD and any limitations arising from IPD that were not available.	
Conclusions	26	Provide a general interpretation of the findings in the context of other evidence.	
Implications	A4	Consider relevance to key groups (such as policy makers, service providers and service users). Consider implications for future research.	
Funding			
Funding	27	Describe sources of funding and other support (such as supply of IPD), and the role in the systematic review of those providing such support.	

A1 – A3 denote new items that are additional to standard PRISMA items. A4 has been created as a result of re-arranging content of the standard PRISMA statement to suit the way that systematic review IPD meta-analyses are reported.

APPENDIX 2. SUMMARY TABLE OF ELIGIBLE STUDIES FOR THIS IPD META-ANALYSIS ALREADY IDENTIFIED

Trial name – Trial registry	Drug – Company	Sample	Follow-Up Duration	Damage	Function	Population
PREMIER - NCT00195663	Adalimumab - Abbvie	799/ 697/ 452	10y	mTSS	HAQ	Naïve MTX
DE019 - NCT00195702	Adalimumab - Abbvie	619/ 202/ 327	10y	mTSS	HAQ	Non-responders MTX
TEAR - NCT00259610	Etanercept - Pfizer	755/476	2y	mTSS	mHAQ	Non-responders MTX
COMET - NCT00195494	Etanercept - Pfizer	542/398	2y	mTSS	HAQ	Naïve MTX
CAMEO - NCT00654368	Etanercept - Pfizer	205	2Y	mTSS	HAQ	Non-responders MTX
PRIZE - NCT00913458	Etanercept - Pfizer	193/131	1,5/2y	mTSS	HAQ	Naïve MTX
TEMPO - NCT00393471	Etanercept - Pfizer	682	3y	mTSS	HAQ	Failed DMARD (not MTX)
PRESERVE - NCT00565409	Etanercept - Pfizer	600	2y (88w)	mTSS	HAQ	Non-responders MTX
ERA - NCT00356590	Etanercept - Pfizer	632/512 ~300	2y 2 + 3y	Sharp	HAQ	Naïve MTX
GO BEFORE - NCT00264537	Golimumab - MSD	637/422	2+3Y	mTSS	HAQ	Naïve MTX
GO FORWARD - NCT00264550	Golimumab - MSD	444/313	5Y	mTSS	HAQ	Non-responders MTX
GO FURTHER - NCT00973479	Golimumab - MSD	592/486	2Y (100w)	mTSS	HAQ	Non-responders MTX
ATTRACT - NCT00269867	Infliximab - MSD	428/340	2y (102w)	mTSS	HAQ	Non-responders MTX
ASPIRE - NCT00236028	Infliximab - MSD	1049	1y	mTSS	HAQ	Non-responders MTX
LITHE - NCT00106535	Tocilizumab - Roche	1190/ 1149	5y	GmTSS	HAQ	Non-responders MTX
FUNCTION - NCT01007435	Tocilizumab - Roche	1157	2y	mTSS	HAQ	Non-responders MTX
BREVACTA - NCT01232569	Tocilizumab - Roche	656/ 314	2Y	mTSS	HAQ	Non-responders MTX
ACT-RAY - NCT00810199	Tocilizumab - Roche	512/423	2Y	GmTSS	HAQ	Non-responders MTX
SAMURAI - NCT00144508	Tocilizumab - Roche	306/241	1y 3y	mTSS	mHAQ	Non-responders MTX
SURPRISE - NCT01120366	Tocilizumab - Roche	226	2Y	mTSS	HAQ	Non-responders MTX
REFLEX - NCT00468546/ NCT02097745	Rituximab - Roche	517 184	2Y 5Y	GmTSS	HAQ	Inadequate response to anti-TNF
IMAGE - NCT00299104	Rituximab - Roche	776/606	2Y	GmTSS	HAQ	Naïve MTX
RAPID 1 - NCT00152386	Certolizumab - UCB	982/847	3y (148w)	mTSS	HAQ	Non-responders MTX
RAPID 2 - NCT00160602/ NCT00175877	Certolizumab - UCB	619/567	2,5y (128w)	mTSS	HAQ	Non-responders MTX
C-OPERA - NCT01451203	Certolizumab - UCB	316/184 131	1y 2y	mTSS	HAQ	Naïve MTX
ORAL START - NCT01039688	Tofacitinib - Pfizer	958/956	2y	mTSS	HAQ	Naïve MTX
ORAL SCAN - NCT00847613	Tofacitinib - Pfizer	797	2y	mTSS	HAQ	Non-responders MTX

DMARD - disease-modifying antirheumatic drugs; GmTSS - Genant-modified Total Sharp Score; HAQ - Health Assessment Questionnaire; mHAQ – modified Health Assessment questionnaire; mTSS - modified Total Sharp Score; MTX - Metotrexate; TNF - tumor necrosis factor

APPENDIX 3. LIST OF VARIABLES REQUIRED AND DESIRABLE FOR ANALYSES

- Remission definition data (minimum at baseline, 6 and 12 months; desired also at 3 and 9 months, 2 years, others)
  - SJC28
  - TJC28
  - CRP (in mg/dl or mg/L, but clearly indicated)
  - PGA
- Outcome data (minimum at baseline, 12 and 24 months; desired 5 and 10 years)
  - Radiographic score
  - HAQ
- Patient characteristics (all at baseline only)
  - gender
  - age at baseline
- Clinical characteristics (all at baseline only)
  - disease duration at baseline
  - RF
  - ACPA (not essential)
  - Treatment arm
- Trial/visit information
  - anonymised patient ID code (at baseline only)
  - visit number or sequence
  - visit date

APPENDIX 4. EXAMPLES OF PATIENT'S CLASSIFICATION IN DIFFERENT REMISSION STATE DEFINITIONS (DICHOTOMIC AND CATEGORICAL) AND CONSIDERING SINGLE OR MULTIPLE TIME POINTS (SUSTAINED REMISSION) FOR ITS ASSESSMENT

A. Example of sub-group determination to compare Likelihood Ratios between 3v and 4v-remission, considering 1 point in time during the first year (6 or 12 months).

	6 months					12-months						
Patient	TJC ≤1	SJC ≤1	CRP ≤1	PGA ≤1	Remission state	TJC ≤1	SJC ≤1	CRP ≤1	PGA ≤1	Remission state	4v-rem at 6 or 12 months?	3v-rem at 6 or 12 months?
1	✔	✔	✔	✗	3v-Rem	✔	✔	✔	✗	3v-Rem	No	Yes
2	✔	✔	✔	✗	3v-Rem	✔	✔	✔	✔	4v & 3v-Rem	Yes	Yes
3	✔	✔	✔	✔	4v & 3v-Rem	✔	✔	✔	✔	4v & 3v-Rem	Yes	Yes
4	✔	✔	✔	✔	4v & 3v-Rem	✔	✔	✔	✗	3v-Rem	Yes	Yes
5	✔	✔	✔	✔	4v & 3v-Rem	✔	✔	✔	✔	4v & 3v-Rem	Yes	Yes
6	✔	✔	✔	✗	3v-Rem	✗	✔	✔	✗	Non-Rem	No	Yes
7	✔	✗	✔	✔	Non-Rem	✔	✔	✔	✔	4v & 3v-Rem	Yes	Yes
8	✗	✗	✔	✗	Non-Rem	✔	✔	✔	✗	3v-Rem	No	Yes
9	✗	✗	✔	✗	Non-Rem	✔	✔	✔	✔	4v-Rem	Yes	Yes
10	✔	✔	✗	✗	Non-Rem	✗	✗	✗	✗	Non-Rem	No	No
11	✗	✗	✔	✔	Non-Rem	✔	✔	✗	✔	Non-Rem	No	No
12	✔	✗	✔	✗	Non-Rem	✗	✔	✔	✗	Non-Rem	No	No
13	✔	✔	✗	✗	Non-Rem	✗	✔	✔	✗	Non-Rem	No	No

Likelihood Ratios will be obtained from the following comparisons for this example:
a) Patients in 4v-Rem vs patient in Non 4v-Rem = 6 vs 7
b) Patients in 3v-Rem vs patient in Non 3v-Rem = 9 vs 4

B. Example of sub-group determination to compare Likelihood Ratios between 3v and 4v-remission, considering sustained remission during the first year (…, 6, …, and 12 months*).

	6 months					12-months					4v-rem sustai-ned rem?	3v-rem sustai-ned rem?
Patient	TJC ≤1	SJC ≤1	CRP ≤1	PGA ≤1	Remission state	TJC ≤1	SJC ≤1	CRP ≤1	PGA ≤1	Remission state		
1	✔	✔	✔	✗	3v-Rem	✔	✔	✔	✗	3v-Rem	No	Yes
2	✔	✔	✔	✗	3v-Rem	✔	✔	✔	✔	4v & 3v-Rem	No	Yes
3	✔	✔	✔	✔	4v & 3v-Rem	✔	✔	✔	✔	4v & 3v-Rem	Yes	Yes
4	✔	✔	✔	✔	4v & 3v-Rem	✔	✔	✔	✗	3v-Rem	No	Yes
5	✔	✔	✔	✔	4v & 3v-Rem	✔	✔	✔	✔	4v & 3v-Rem	Yes	Yes
6	✔	✔	✔	✗	3v-Rem	✗	✔	✔	✗	Non-Rem	No	No
7	✔	✗	✔	✔	Non-Rem	✔	✔	✔	✔	4v & 3v-Rem	No	No
8	✗	✗	✔	✗	Non-Rem	✔	✔	✔	✗	3v-Rem	No	No
9	✗	✗	✔	✗	Non-Rem	✔	✔	✔	✔	4v-Rem	No	No
10	✔	✔	✗	✗	Non-Rem	✗	✗	✗	✗	Non-Rem	No	No
11	✗	✗	✔	✔	Non-Rem	✔	✔	✗	✔	Non-Rem	No	No
12	✔	✗	✔	✗	Non-Rem	✗	✔	✔	✗	Non-Rem	No	No
13	✔	✔	✗	✗	Non-Rem	✗	✔	✔	✗	Non-Rem	No	No

Likelihood Ratios will be obtained from the following comparisons for this example :
a) Patients in sustained 4v-Rem vs patient in Non sustained 4v-Rem = 2 vs 11
b) Patients in sustained 3v-Rem vs patient in Non sustained 3v-Rem = 5 vs 7

* Only 2 time points are presented in this example (6 and 12 months), however, if they were more (e.g. 3, 6, 9 and 12 months) the same principle of decision would be applied: to be in 4v-rem a patient need to present the criteria in all considered visits, the same for Near-rem. Patients not classified in sustained 4v-rem neither in sustained near-rem would be classified in non sustained rem

C. Example of sub-group determination to compare Likelihood Ratios between 4v and 3v-non-4v-remission, considering 1 point in time during the first year (6 or 12 months).

	6 months					12-months					4v-rem at 6 or 12 months?	3v-rem at 6 or 12 months?
Patient	TJC ≤1	SJC ≤1	CRP ≤1	PGA ≤1	Remission state	TJC ≤1	SJC ≤1	CRP ≤1	PGA ≤1	Remission state		
1	✔	✔	✔	✗	3v-Rem	✔	✔	✔	✗	3v-Rem	No	Yes
2	✔	✔	✔	✗	3v-Rem	✔	✔	✔	✔	4v & 3v-Rem	Yes	Yes
3	✔	✔	✔	✔	4v & 3v-Rem	✔	✔	✔	✔	4v & 3v-Rem	Yes	Yes
4	✔	✔	✔	✔	4v & 3v-Rem	✔	✔	✔	✗	3v-Rem	Yes	Yes
5	✔	✔	✔	✔	4v & 3v-Rem	✔	✔	✔	✔	4v & 3v-Rem	Yes	Yes
6	✔	✔	✔	✗	3v-Rem	✗	✔	✔	✗	Non-Rem	No	Yes
7	✔	✗	✔	✔	Non-Rem	✔	✔	✔	✔	4v & 3v-Rem	Yes	Yes
8	✗	✗	✔	✗	Non-Rem	✔	✔	✔	✗	3v-Rem	No	Yes
9	✗	✗	✔	✗	Non-Rem	✔	✔	✔	✔	4v-Rem	Yes	Yes
10	✔	✔	✗	✗	Non-Rem	✗	✗	✗	✗	Non-Rem	No	No
11	✗	✗	✔	✔	Non-Rem	✔	✔	✗	✔	Non-Rem	No	No
12	✔	✗	✔	✗	Non-Rem	✗	✔	✔	✗	Non-Rem	No	No
13	✔	✔	✗	✗	Non-Rem	✗	✔	✔	✗	Non-Rem	No	No

All patient in non-3v rem are excluded

Likelihood Ratios will be obtained from the following comparisons for this example:
a) Patients in 4v-Rem vs patients in 3v Rem & Non 4v-Rem = 6 vs 3

D. Example of patient's classification in 4v-remission, near-remission and non-remission, considering 1 point in time during the first year (6 or 12 months).

Patient	6 months					12-months					"Best" remission state at 6 or 12 months?
	TJC ≤1	SJC ≤1	CRP ≤1	PGA ≤1	Remission state	TJC ≤1	SJC ≤1	CRP ≤1	PGA ≤1	Remission state	
1	✔	✔	✔	✗	Near-Rem	✔	✔	✔	✗	Near-Rem	Near-Rem
2	✔	✔	✔	✗	Near-Rem	✔	✔	✔	✔	4v-Rem	4v-Rem
3	✔	✔	✔	✔	4v-Rem	✔	✔	✔	✔	4v-Rem	4v-Rem
4	✔	✔	✔	✔	4v-Rem	✔	✔	✔	✗	Near-Rem	4v-Rem
5	✔	✔	✔	✔	4v-Rem	✔	✔	✔	✔	4v-Rem	4v-Rem
6	✔	✔	✔	✗	Near-Rem	✗	✔	✔	✗	Non-Rem	Near-Rem
7	✔	✗	✔	✔	Non-Rem	✔	✔	✔	✔	4v-Rem	4v-Rem
8	✗	✗	✔	✗	Non-Rem	✔	✔	✔	✗	Near-Rem	Near-Rem
9	✗	✗	✔	✗	Non-Rem	✔	✔	✔	✔	4v-Rem	4v-Rem
10	✔	✔	✗	✗	Non-Rem	✗	✗	✗	✗	Non-Rem	Non Rem
11	✗	✗	✔	✔	Non-Rem	✔	✔	✗	✔	Non-Rem	Non Rem
12	✔	✗	✔	✗	Non-Rem	✗	✔	✔	✗	Non-Rem	Non Rem
13	✔	✔	✗	✗	Non-Rem	✗	✔	✔	✗	Non-Rem	Non Rem

E. Example of patient's classification in 4v-remission, near-remission and non-remission, considering sustained remission during the first year (…, 6, ..., and 12 months*).

Patient	6 months					12-months					"Best" sustained remission state at … 6, …, and 12 months?
	TJC ≤1	SJC ≤1	CRP ≤1	PGA ≤1	Remission state	TJC ≤1	SJC ≤1	CRP ≤1	PGA ≤1	Remission state	
1	✔	✔	✔	✗	Near-Rem	✔	✔	✔	✗	Near-Rem	Sust. Near-Rem
2	✔	✔	✔	✗	Near-Rem	✔	✔	✔	✔	4v-Rem	Sust. Near-Rem
3	✔	✔	✔	✔	4v-Rem	✔	✔	✔	✔	4v-Rem	Sust. 4v-Rem
4	✔	✔	✔	✔	4v-Rem	✔	✔	✔	✗	Near-Rem	Sust. Near-Rem
5	✔	✔	✔	✔	4v-Rem	✔	✔	✔	✔	4v-Rem	Sust. 4v-Rem
6	✔	✔	✔	✗	Near-Rem	✗	✔	✔	✗	Non-Rem	Non Sust. Rem
7	✔	✗	✔	✔	Non-Rem	✔	✔	✔	✔	4v-Rem	Non Sust. Rem
8	✗	✗	✔	✗	Non-Rem	✔	✔	✔	✗	Near-Rem	Non Sust. Rem
9	✗	✗	✔	✗	Non-Rem	✔	✔	✔	✔	4v-Rem	Non Sust. Rem
10	✔	✔	✗	✗	Non-Rem	✗	✗	✗	✗	Non-Rem	Non Sust. Rem
11	✗	✗	✔	✔	Non-Rem	✔	✔	✗	✔	Non-Rem	Non Sust. Rem
12	✔	✗	✔	✗	Non-Rem	✗	✔	✔	✗	Non-Rem	Non Sust. Rem
13	✔	✔	✗	✗	Non-Rem	✗	✔	✔	✗	Non-Rem	Non Sust. Rem

* Only 2 time points are presented in this example (6 and 12 months), however, if they were more (e.g. 3, 6, 9 and 12 months) the same principle of decision would be applied: to be in 4v-rem a patient need to present the criteria in all considered visits, the same for Near-rem. Patients not classified in sustained 4v-rem neither in sustained near-rem would be classified in non sustained rem

Manuscript 10

Revisiting the treatment targets of remission for rheumatoid arthritis by excluding patient global assessment: an analysis based on data from 11 RCTS and 5792 patients.

Ferreira RJO, Welsing PW, Jacobs JWG, Gossec L, Ndosi M, Machado PM, van der Heijde D, da Silva JAP

(Submitted)

Revisiting the treatment targets of remission for rheumatoid arthritis by excluding patient global assessment: an analysis based on data from 11 RCTs and 5792 patients.

Authors:

Ricardo J. O. Ferreira[1,2*], Paco M. J. Welsing[3*], Johannes W. G. Jacobs[4], Laure Gossec [5,6], Mwidimi Ndosi[7], Pedro M. Machado[8,9,10], Désirée van der Heijde[11], José A. P. da Silva [1, 12]

* Contributed equally to this work

Affiliations:

1 – Rheumatology department – Centro Hospitalar e Universitário de Coimbra EPE, Coimbra, Portugal.

2 – Health Sciences Research Unit: Nursing (UICISA: E), Nursing School of Coimbra, Coimbra, Portugal; rferreira@reumahuc.org

3 – Department of Rheumatology & Clinical Immunology – University Medical Center, Utrecht, The Netherlands.

4 – Department of Rheumatology & Clinical Immunology – University Medical Center, Utrecht, The Netherlands.

5 – Sorbonne Université – Institut Pierre Louis d'Epidémiologie et de Santé Publique, INSERM, Paris France.

6 – Rheumatology department – Pitié Salpêtrière hospital, AP-HP, Paris, France.

7 – Department of Nursing and Midwifery – University of the West of England, Bristol, UK.

8 – Centre for Rheumatology & MRC Centre for Neuromuscular Diseases – University College London, London, UK.

9 – Department of Rheumatology, University College London Hospitals NHS Foundation Trust, London, UK.

10 – Department of Rheumatology – Northwick Park Hospital, London North West University Healthcare NHS Trust, London, UK.

11 – Rheumatology department – Leiden University Medical Centre, Leiden, The Netherlands.

12 – Clínica Universitária de Reumatologia, and i-CBR Coimbra Institute for Clinical and Biological Research, Faculty of Medicine - University of Coimbra, - Portugal; jdasilva@chuc.min-saude.pt

Corresponding author: José António P. da Silva, MD, PhD

Rheumatology Department, Centro Hospitalar Universitário de Coimbra, EPE.

Praceta Professor Mota Pinto, 3000-075 Coimbra. Portugal

Phone: 00351 239400547 Fax: 00351 239400587 e-mail: jdasilva@chuc.min-saude.pt

Keywords: *Rheumatoid arthritis, outcomes research, patient global assessment, patient reported outcomes, disease activity, remission, near-remission, radiographic damage, individual patient data meta-analysis.*

Abstract

Objectives: To determine the influence on radiographic outcome of patient global assessment (PGA) in the ACR/EULAR Boolean remission criteria, in patients with rheumatoid arthritis (RA).

Methods: Individual patient data meta-analysis of randomized controlled trials of biological agents. Remission was classified using the ACR/EULAR remission criteria with 4 variables: (i) tender and swollen 28-joint counts (TJC28/SJC28) both≤1, C-reactive protein (CRP)≤1 mg/dl, and PGA≤1 (0-10=worst) (4V-remission), (ii) the same except PGA>1 (PGA-near-remission) (iii) 3V-remission (the two previous ones combined, similar to 4V, but without PGA) and (iv) non-remission.

The relationship between the most stringent remission class present at 6 or 12 months and radiographic progression during the second year was analysed. Good radiographic outcome (GRO) was defined as an increase of ≤0.5 in the Sharp/van der Heijde score. The pooled probabilities of GRO for the different definitions of remission were estimated and compared.

Results: Eleven trials, 5,792 patients were analysed. 4V-remission was achieved by 23% of patients and PGA-near-remission by 19%. The probability of GRO in the PGA-near-remission group was similar to that of 4V-remission (78.2 vs 81.1 %, ns) but significantly higher than that for non-remission (71.8%; difference 6%; 95%CI 2 to 10%). 3V-remission showed higher predictive accuracy for GRO (51%, 95%CI 47 to 55%) than 4V-remission (41%, 95%CI 35 to 46%).

Conclusion: PGA-near-remission and 3V-remission have similar validity as the original 4V-remission definition in predicting GRO, while potentially reducing the risk of overtreatment.

This supports the use of 3V-remission as the target for immunosuppressive therapy, and the use of separate measures to assess disease impact: a dual-target approach.

Systematic review registration: PROSPERO, CRD42017057099.

KEY MESSAGES

- From a pooled analysis of 11 clinical trials in rheumatoid arthritis (RA), 23.0% of 5,792 patients achieved ACR/EULAR Boolean-based remission at 6 or 12 months, while 18.9% did not reached this target status solely due to a patient global assessment (PGA)>1/10 ("PGA-near-remission")
- The rate of good radiographic outcome (≤0.5 units progression over the second year) did not differ significantly between patient in PGA-near-remission (78.2%; 95%CI: 69.5 to 85.8%) and patients in "full" 4V-remission (81.1%; 74.4 to 86.9%).
- Excluding PGA from the ACR/EULAR Boolean-based definition of remission (i.e. 3V-remission) increased the percentage of correctly classified patients as having and not having radiographic damage progression.

INTRODUCTION

Disease remission has become the guiding target in the management of rheumatoid arthritis (RA), as it conveys the best possible outcomes [1]. Current treatment recommendations advise that remission (or at least low disease activity) should be attained as soon and as consistently as possible, and changes in treatment should be considered when this does not happen [2, 3].

The most influential and authoritative definition of remission was published in 2011 under the auspices of the American College of Rheumatology (ACR), the European League Against Rheumatology (EULAR) and the Outcome Measures in Rheumatology (OMERACT) groups.[4] A Boolean-based definition was endorsed: and requires that scores of tender and swollen 28-joint counts (TJC28 and SJC28), C-Reactive Protein (CRP, in mg/dl), and patient global assessment of disease activity (PGA, 0–10 scale) are all ≤1.[4]

The inclusion of PGA in the definitions of remission in RA was justified because it added predictive value for later good radiographic and functional outcomes, while conveying the much-needed patient's perspective.[4]

Despite this, the inclusion of PGA remains controversial.[5-9] Using the definitions above, studies in different clinical practice cohorts,[10-15] have reported that as many as 10% [13] to 38% [14] of all patients with RA, do not reach remission solely due to a PGA score >1, a state that has become designated as "PGA-near-remission".[14, 16] Moreover, it has been demonstrated that PGA bears little relationship with markers of the disease process, which drives structural damage, rather reflecting pain, fatigue and function. [9, 17, 18] This is especially evident when analyses are restricted to the lower levels of disease activity, in the range where the definition of remission has a decisive impact on whether to maintain or to escalate immunosuppressive treatment. According to this perspective, patients in PGA-near-remission would not benefit from additional immunosuppression, as this cannot be expected

to improve their condition or foster remission,[9, 17] and are exposed by current recommendations to the risk of overtreatment and unjustified side-effects.[19]

These observations have led to the suggestion that the patients' interest would be better served by the adoption of two separate complementary targets: the first focused on remission of the inflammatory process, guided by an instrument without PGA; the second focused only on patient-reported impact measures.[9, 16, 20] However, this proposal would not be sustainable if, as suggested in the original ACR/EULAR/OMEARCT paper, removing PGA from the Boolean-based remission significantly diminishes its ability to predict good radiographic outcome.[4] A systematic literature review (SLR) indicated that, among the individual components included in the definitions of remission, only swollen joints and acute phase reactants are associated with radiographic progression.[21] To date, only one study (BARFOT, n=527) compared the prediction of good radiographic outcome by "4V-remission" versus "3V-remission" (without PGA) achieved in early RA patients: no significant differences were observed, but the two groups were not mutually exclusive.[13] No study has ever compared the radiographic outcomes between the 4V-remission and PGA-near-remission groups.

The primary aim of this study was to compare PGA-near-remission and 4V-remission regarding their association with radiographic damage progression. Secondarily, we aimed to explore the impact of using 3V- instead of 4V-remission in patients with RA, both in terms of prevalence of remission and association with structural damage progression.

METHODS

Design and study selection

This was an individual patient data meta-analysis of published randomized controlled trials (RCTs) selected through a systematic literature review. The study protocol was registered in PROSPERO with the number CRD42017057099 [22] and published elsewhere.[23]

RCTs were included if they tested the efficacy of biological disease-modifying antirheumatic drugs (bDMARDs) on ≥2-year radiographic outcomes, in patients fulfilling the 1987 ACR or the 2010 ACR-EULAR criteria for RA.[24, 25] Information on the processes of identifying and selecting studies, as well collecting data are reported in the protocol.[23]

Specification of outcomes

Primary outcome

The primary outcome of this study was the percentage of individuals with a good radiographic outcome (GRO) during the second year of the trial (i.e. between month 12 and month 24), defined as:

i. a change (Δ) ≤0.5 units in the van der Heijde modified-Total Sharp Scores (mTSS)[26].

This ≤0.5 cut-off has been preferred [27-29] over the one used in the ACR/EULAR pivotal publication (≤0 cut-off), because 0.5 is the preferred cut-off if the average of two readers is used.[30]

Secondary outcomes

Two additional/secondary endpoint cut-offs were used to define good radiographic outcome during the second year of the trial:

ii. ΔmTSS≤5 units, a higher, frequently used rate (sometimes referred to as rapid radiographic progression;

iii. ΔmTSS≤0 units, to allow comparisons with the results obtained by the ACR/EULAR study [4].

Comparisons: mutually and non-mutually exclusive definitions of remission

Analyses were based on different definitions of remission states, assessed at two time points, 6 months and 12 months, following the methodology adopted by the ACR/EULAR committee[4], as follows:

a) ACR/EULAR Boolean-based remission [4], also designed in this study as "4V-Remission" (i.e., TJC28≤1, SJC28≤1, CRP≤1 mg/dl, and PGA≤1/10)
b) "PGA-near-remission"[11, 14], defined as TJC28≤1, SJC28≤1, CRP≤1 mg/dl, and PGA>1.
c) "Non-remission" defined as TJC28>1 or SJC28>1 or CRP>1 mg/dl, irrespective of PGA value.

The above three definitions are mutually exclusive, i.e. each patient will be categorized in one group only.

d) "3V-remission" defined as TJC28≤1, SJC28≤1, CRP≤1 mg/dl. This is actually a combination of 4V-remission and PGA-near-remission - patients classified in 4V-remission also meet the 3V-remission criteria.

All definitions of remission were considered fulfilled if they were achieved at 6 OR 12 months' follow-up and patients were classified according to the most stringent definition they satisfied (for instance, if a patient was in PGA-near-remission at 6 months and in 4V-remission at 12 months, he/she was classified as in 4V-remission).

Data analysis and synthesis

Data analysis

For each trial we determined the number of patients with GRO in each remission group (4V-remission, PGA-near-remission, 3V remission and non-remission). The rates of true positive (TP) i.e. remission and GRO, true negative (TN) i.e. non-remission and not-GRO, false negative (FN) i.e. non-remission and GRO, and false positive (FP) i.e. remission and not-

GRO cases were also determined for all definitions of remission. The percentage of correctly classified patients as having and not having GRO were also determined (sum of TP and TN) for the 4V- and 3V-remission.

Missing data was not substituted by any method of data imputation.

Meta-analysis

Frequency of remission status and outcomes

The frequency/proportion (and 95% CI) of each remission state observed in each of the trials were meta-analysed, irrespective of the treatment arm. The same procedure was used to determine the pooled prevalence of GRO according to remission status.

Likelihood of reaching good radiographic outcomes for PGA-near-remission compared to 4V-remission and to non-remission

To test the validity of PGA as part of the definition of remission, our main analysis, we determined and compared the pooled differences in the proportion/chance (Δ proportion) of GRO (ΔmTSS≤0.5) between PGA-near-remission and 4V-remission. We also compared this between PGA-near-remission and non-remission states. The OR (95%CI) for GRO between these groups were also calculated.

Sensitivity analyses

Multivariate logistic regressions were performed in each trial to explain GRO (dependent variable) using the mutually exclusive remission states as independent variables, adjusted for important covariates at baseline: gender, age, disease duration (except for three trials due to >50% of missing data in this covariate), rheumatoid factor status, level of radiographic damage, and treatment arm. The OR obtained in each trial and its 95%CI, and standard

error, obtained were meta-analysed to obtain the pooled OR of GRO comparing different mutually-exclusive remission states.

However, we hypothesise that this covariate adjustment may constitute an overcorrection, because patients in remission are 'naturally' different from patients not in remission regarding these prognostic factors. For this reason, these sensitivity analyses are presented cautiously and only in supplementary material.

Likelihood of reaching good radiographic outcomes with 4V-remission compared to 3V-remission

If the null hypothesis of this study (the chance of GRO in PGA-near-remission group are similar to the 4V-remission group) is not rejected, the current 4V-remission and the proposed 3V-remission can be compared in terms of their positive (LR+) and negative likelihood ratios (LR-) of GRO per remission group. The TP, TN, FN, and FP values were used to synthesize these measures.

Further details of primary data analyses and meta-analyses can be found in Supplementary File S1.

RESULTS

Studies and participants

From a total of 27 identified studies, we were granted access to 17 through secure online platforms, but only 11 trials reported radiographic damage progression during the second year, thus allowing inclusion in the final analyses. The flow diagram of studies and population, with reasons for exclusion, is presented in Supplementary Figure S1. We had access to data from 100% of the randomized patients in 9 out of the 11 trials and from 93% of patients in the remaining three, resulting in a total sample of 8,114 patients. Most trials tested anti-TNFα therapies (n=9), and included patients with insufficient response to MTX

(n=7) and with established disease (>2 years) (n=9) - Supplementary Table S1. The mean (SD) DAS28CRP3v ranged from 4.7 (1.1) to 5.3 (0.8) at baseline. The van der Heijde mTSS was used as the scoring method of radiographic damage progression in 10 of the trials. The remaining used the Genant method. The mean mTSS at baseline ranged from 6.1 (14.6) to 68.3 (55.2) (Supplementary Table S1).

Frequency of remission status and radiographic outcomes

A total of 5,792 (71%) patients had information on both the remission definition and on the primary outcome (radiographic progression) (Table 1). Pooled meta-analytic frequency (95% CI) of 4V-remission at 6 OR 12 months was 23.0% (18.0 to 28.0%), while for PGA-near-remission was 18.9% (15.4 to 22.1%), considering all treatment arms together (Table 1). In four studies the rate of PGA-near-remission was higher than the rate of 4V-remission. Among these four studies, three were the most recently published and had the shorter mean duration of disease (Supplementary Table S1).

Good radiographic outcome was observed in 74.1% (66.2 to 82.0%) of all patients using the primary cut-off (ΔmTSS≤0.5), and by 94.6% (92.9 to 96.4%) using ΔmTSS≤5. (Table 1).

Table 1 Frequency of remission and good radiographic outcome in the included studies

Trial (year)	n [a]	Remission at 6 OR 12 months, n (%)			Good Radiographic outcome from 12 to 24 months [b], n (%)		
		4V-remission	PGA-near-remission	Non-remission	ΔmTSS≤0	ΔmTSS≤0.5	ΔmTSS≤5
DE019 (2004)	844	308 (36.5)	151 (17.9)	385 (45.6)	713 (84.5)	766 (90.8)	840 (99.5)
TEMPO (2004)	540	156 (28.9)	50 (9.3)	334 (61.8)	286 (53.0)	351 (65.0)	483 (89.4)
COMET (2008)	425	68 (16.0)	45 (10.6)	312 (73.4)	245 (57.6)	297 (69.9)	397 (93.4)
RAPID 1 (2008)	650	177 (27.2)	143 (22.0)	330 (50.8)	424 (65.2)	508 (78.2)	636 (97.7)
RAPID 2 (2009)	417	51 (12.2)	81 (19.4)	285 (68.4)	286 (68.6)	324 (77.7)	398 (95.4)
GO-FORWARD (2010)	352	86 (24.4)	74 (21.0)	192 (54.6)	200 (56.8)	228 (64.8)	304 (86.4)
GO-BEFORE (2011)	499	117 (23.5)	80 (16.0)	302 (60.5)	403 (80.8)	446 (89.4)	493 (98.8)
LITHE (2011)	442	113 (25.6)	91 (20.6)	238 (53.8)	282 (63.8)	330 (74.7)	423 (95.7)
DE013 (2013)	796	146 (18.3)	174 (21.9)	476 (59.8)	558 (70.1)	640 (80.4)	790 (99.2)
GO-FURTHER (2014)	483	54 (11.2)	89 (18.4)	340 (70.4)	151 (31.3)	191 (39.5)	405 (83.9)
FUNCTION (2016)	344	102 (29.7)	107 (31.1)	135 (39.2)	250 (72.7)	289 (84.0)	329 (95.6)
Total n	5,792	1,378	1,085	3,329	3,798	4,370	5,498
Meta-analytic % (95% CI)		23.0 (18.0, 28.0)	18.9 (15.4, 22.1)	58.1 (52.0, 64.1)	64.1 (54.9, 73.2)	74.1 (66.2, 82.0)	94.6 (92.9, 96.4)

a. Number of patients with information both on remission status and on radiographic outcome

b. All trials used van der Heijde mTSS except the LITHE trial, in which the Genant mTSS was used instead.

Legend: 4V-remission = SJC28, TJC28, CRP (in mg/dl), and PGA (0-10), all ≤1; PGA-near-remission= SJC28, TJC28, CRP (in mg/dl) ≤1 and PGA (0-10)>1; Non-remission = SJC28 >1 OR TJC28>1 OR CRP (in mg/dl)>1 at 6 OR 12 months of follow-up in all cases; ΔmTSS = change in the modified Total Sharp Score during the second year of follow-up

Likelihood of reaching good radiographic outcome for patients in PGA-near-remission compared to patients in 4V-remission and to patients in non-remission

Overall, the proportion of GRO for the primary score (∆mTSS≤0.5) was high (71.8 to 81.1%) for the three mutually-exclusive remission categories (Table 2). The proportion of patients with GRO did not differ significantly between those in PGA-near-remission and 4V-remission: -2.9% (95%CI: -7.3 to +1.5%). Patients in PGA-near-remission had a significantly higher chance of achieving GRO compared to patients in non-remission (+6.2%; 95%CI: 2.3 to 10.1%). Results for these comparisons are shown in Table 2 and Figure 1. Similar observations were made for GRO defined as ∆mTSS≤5 (Table 2). None of the differences was statistically significant when ∆mTSS≤0 was used (Table 2).

Table 2: Pooled meta-analytic outcomes and association measures for remission categories reached at 6 OR 12 months and good radiographic outcome, during the second year of follow-up.

	Good Radiographic Outcome (GRO) defined as ∆**mTSS≤0.5**		
	4V-remission	***PGA-near-remission***	***Non-remission***
Proportion GRO, % (CI 95%)	81.1% (74.4% to 86.9%)	78.2% (69.5% to 85.8%)	71.8% (62.1% to 80.5%)
	PGA-near-remission vs 4V-remission		***PGA-near-remission vs Non-remission***
∆ Proportion GRO, % (CI 95%)	−2.9% (−7.3% to 1.5%)		6.2% (2.3% to 10.1%)
Odds Ratio GRO (CI 95%)	0.86 (0.68 to 1.07)		1.33 (1.11 to1.60)
	Good Radiographic Outcome (GRO) defined as ∆**mTSS≤0**		
	4V-remission (n=1,378)	***PGA-near-remission (n=1,085)***	***Non-remission (n=3,329)***
Proportion GRO, % (CI 95%)	71.5% (63.5% to 78.8%)	64.1% (54.6% to 73.2%)	62.2% (51.5% to 72.4%)
	PGA-near-remission vs 4V-remission		***PGA-near-remission vs Non-remission***
∆ Proportion GRO, % (CI 95%)	-7.7% (-16.6% to 1.1%)		1.7% (-8.1% to 11.5%)
Odds Ratio GRO (CI 95%)	0.72 (0.49 to 1.04)		1.07 (0.70 to 1.64)
	Good Radiographic Outcome (GRO) defined as ∆**mTSS≤5**		
	4V-remission	***PGA-near-remission***	***Non-remission***
Proportion GRO, % (CI 95%)	97.5% (95.4% to 98.9 %)	96.1% (92.5% to 98.5%)	94.2 % (90.2% to 97.2%)
	PGA-near-remission vs 4V-remission		***PGA-near-remission vs Non-remission***
∆ Proportion GRO, % (CI 95%)	-2.5% (-7.5% to 2.6%)		4.1% (0.7% to 7.6%)
Odds Ratio GRO (CI 95%)	0.67 (0.41 to 1.08)		1.20 (0.85 to 1.69)

Legend: 4V-remission = SJC28, TJC28, CRP (in mg/dl), and PGA (0-10), all ≤1; PGA-near-remission= SJC28, TJC28, CRP (in mg/dl) ≤1 and PGA (0-10)>1; Non-remission = SJC28 >1 OR TJC28>1 OR CRP (in mg/dl)>1, irrespective of PGA value; at 6 OR 12 months of follow-up in all cases; ∆mTSS = change in the modified Total Sharp Score during the second year of follow-up; GRO = Good Radiographic Outcome.

Figure 1. Meta-analyses of Odds Ratio of having good radiographic outcome (ΔmTSS≤0.5 units) when in PGA-near-remission vs 4V-remission and Non-remission.

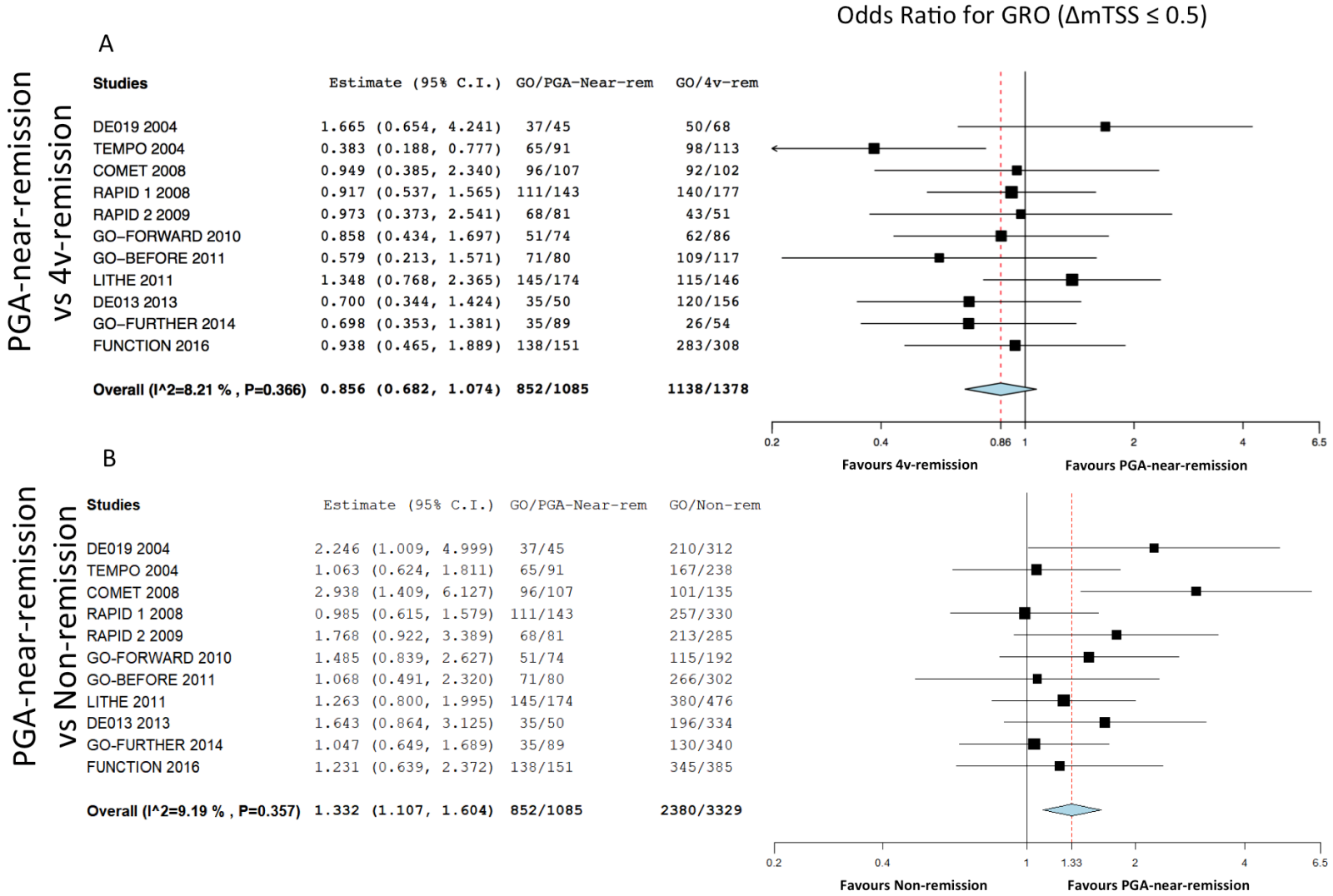


Figure legend: 4V-remission = SJC28, TJC28, CRP (in mg/dl), and PGA (0-10), all ≤1; PGA-near-remission= SJC28, TJC28, CRP (in mg/dl) ≤1 and PGA (0-10)>1; Non-remission = SJC28 >1 OR TJC28>1 OR CRP (in mg/dl)>1, irrespective of PGA value; at 6 OR 12 months of follow-up in all cases; ΔmTSS = change in the modified Total Sharp Score during the second year of follow-up

Comparison of the 4V-remission and the proposed 3V-remission regarding prediction accuracy for radiographic outcome

Having shown that the difference in the probability of GRO between 4v-remission and PGA—near-remission, was neither statistically nor clinically relevant, we evaluated the difference between the 4V-remission and 3V-remission (the latter combining the PGA-near-remission and 4V-remission) groups (Table 3). The results indicated that the likelihood ratio of having GRO (ΔmTSS≤0.5) was higher for patients in 4V-remission compared to 4V-non-remission (LR+=1.36, 1.15 to 1.61) than between patients in 3V-remission vs 3V-non-remission (LR+=1.26; 1.13 to 1.41), although there was a large overlap in 95%CIs. Conversely, the likelihood of having GRO in the absence of remission was significantly smaller for the 3V-remission (LR-=0.86; 0.79 to 0.94) and non-significant for the 4V-remission (LR-=0.92; 0.81 to 1.04) vs their counterparts (Table 3).

Table 3. Meta-analyses of good outcome likelihood ratios for the 4V- and 3V-remission status (n=5,792)

Good Outcome	**4V-Remission** (versus non-4V)		I^2 LR+ LR-	**3V-Remission** (versus non-3V)		I^2 LR+ LR-
	LR+ (95% CI)	LR- (95% CI)		LR+ (95% CI)	LR- (95% CI)	
ΔmTSS≤ 0.5	1.36 (1.15 to 1.61)	0.92 (0.81 to 1.04)	38% 0%	1.26 (1.13 to 1.41)	0.86 (0.79 to 0.94)	40% 3%
ΔmTSS≤ 0	1.32 (1.17 to 1.50)	0.91 (0.82 to 1.02)	19% 0%	1.20 (1.12 to 1.29)	0.87 (0.81 to 0.93)	0% 0%
ΔmTSS≤ 5	1.40 (0.88 to 2.23)	1.01 (0.76 to 1.33)	56% 0%	1.33 (1.03 to 1.71)	0.92 (0.77 to 1.10)	40% 0%

Legend: 4V-remission = SJC28, TJC28, CRP (in mg/dl), and PGA (0-10), all ≤1; 3V-remission= SJC28, TJC28, CRP (in mg/dl) ≤1; Non-remission = SJC28 >1 OR TJC28>1 OR CRP (in mg/dl)>1, irrespective of PGA value; at 6 OR 12 months of follow-up in all cases ΔmTSS = change in the modified Total Sharp during the second year of follow-up. LR+ = Positive Likelihood Ratio; LR- = Negative Likelihood Ratio. I^2: heterogeneity index.

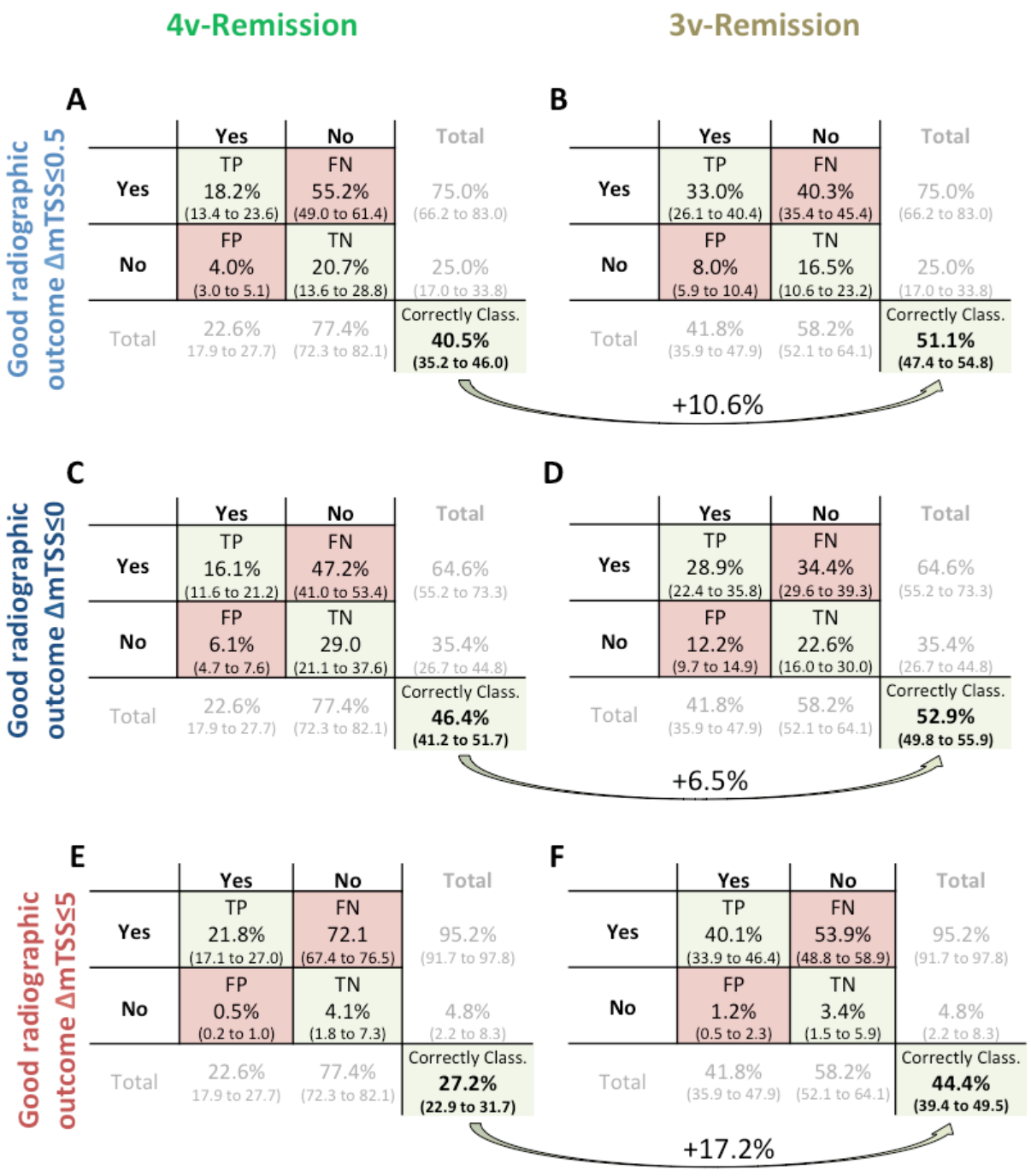
The proportion of patients that were correctly classified (= TP + TN) was, overall, quite low for both definitions of remission (≤53%). It was, however, 10.6% and 17.2% higher with the

3V-remission than with the 4V-remission definitions, for ΔmTSS≤0.5 and ΔmTSS≤5, respectively (Figure 2A-B versus 2E-F).

Figure 3 presents a "clinical eye's" summary of good/bad radiographic outcomes observed according to the current and the proposed (3V) Boolean-based definitions of remission (95%CI and I^2 statistics are presented in Supplementary Table S2). Overall, 73.3% (95%CI: 63.9% to 81.8%) of the patients in non-4V-remission still had GRO (ΔmTSS≤0.5), and the same was observed for 71.8% (95%CI: 62.1% to 80.5%) of those in non-3V-remission. The percentages of GRO increase to 81.1% (95%CI: 74.4% to 86.9%) and 79.6% (95%CI: 72.2% to 86.1%) among those in 4V and 3V-remission, respectively. None of these differences were statistically significant.

The overall proportion of patients achieving 3V-remission was almost double of those reaching 4V-remission (41.9% vs 23.0%).

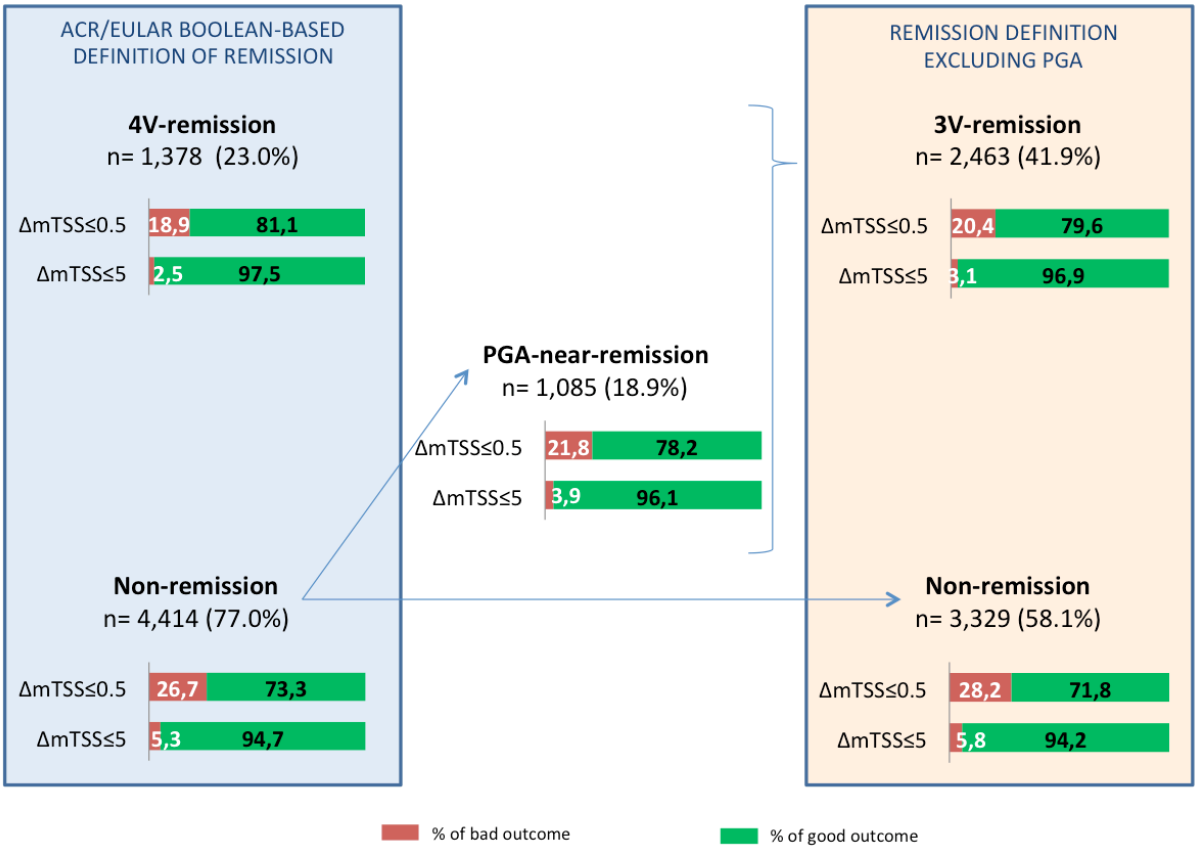
Figure 2 – Pooled meta-analytic prediction accuracy of 4V- and 3V-remission status for the good radiographic outcome (n=5,792)



Legend: 4V-remission = SJC28, TJC28, CRP (in mg/dl), and PGA (0-10), all ≤1; 3V-remission= SJC28, TJC28, CRP (in mg/dl) ≤1; ΔmTSS = change in the modified Total Sharp Score from 12 months to 24 months. TP = True Positive; TN = True Negative; FP = False Positive; FN = False Negative; Correctly classified = TP + TN.

The sum of the meta-analytic percentages of TP, FN, FP, and TN is slightly less than 100% due to error estimation when multi-category (k>2) prevalence is estimated.[32] All meta-analyses used double arcsine transformation as the preferred method to correct this situation. [32]

Figure 3 – Reclassification of remission status and respective radiographic outcomes (n=5,792). Percentages were calculated through meta-analyses.



Note: Confidence intervals and I^2 statistics of pooled radiographic outcomes can be found in Supplementary Table S2.

Legend: 4V-remission = SJC28, TJC28, CRP (in mg/dl), and PGA (0-10), all ≤1; PGA-near-remission= SJC28, TJC28, CRP (in mg/dl) ≤1 and PGA (0-10)>1; Non-remission = SJC28 >1 OR TJC28>1 OR CRP (in mg/dl)>1, irrespective of PGA value; 3V-remission= SJC28, TJC28, CRP (in mg/dl) ≤1; All definitions as observed at 6 OR 12 months. ΔmTSS = change in the modified Total Sharp Score during the second year of follow-up.

Sensitivity analyses: adjustment to co-factors

The models adjusted for co-factors for the same comparisons showed even smaller differences between PGA-near-remission and 4V-remission categories regarding the prediction of good radiographic outcomes (Supplementary Tables S3 and S4).

DISCUSSION

This is the first study assessing the prevalence of PGA-near-remission in RCTs and the first comparing radiographic damage progression between patients in PGA-near-remission and in 4V-remission. The pooled rate of PGA-near-remission was almost the same of 4V-remission (19% vs 23%). These mutually exclusive groups did not differ significantly in terms of subsequent radiographic damage accrual. Patients in PGA-near-remission had a significantly better radiographic outcome than those in non-remission.

These observations legitimised the next step in our analyses: to explore the implications of choosing between the 3V and the 4V definitions of remission. The odds of good structural outcome were slightly higher for the 4V-remission, but without statistical, or, in our view, clinical significance. The 3V-remission showed a better performance in terms of true estimations of significant damage (i.e. sum of TP and TN estimations). Adopting the 3V definition of remission as target, as opposed to the 4V, in this population would have avoided therapy escalation in 18.9% of all participants, if not reaching the 4V-remission target leads to treatment escalation, as recommended. This is also rooted in solid clinical common sense: patients who fail remission solely because of PGA should not be expected to benefit from additional immunosuppressive therapy, as the disease process is already under control. Although it might be argued that wise clinicians would not increment therapy in such cases, it is certainly appropriate that guiding definitions and recommendations are aligned with wisdom.

The data also emphasizes that both remission concepts have a relatively poor predictive value regarding radiographic damage, as reflected by low LRs. This reflects the fact that 73% of patients in non-4V-remission had good radiographic outcomes and 19% of those in 4V-remission still presented radiographic progression (ΔmTSS $\leq$0.5).

The robustness of this work is supported by (i) the use of individual patient data, allowing uniform analyses procedures, (ii) the availability of data collected under stringent RCT conditions, (iii) the inclusion of over 5,700 patients, and (iv) the use of both crude and adjusted statistical analyses. This study also has potential limitations and biases. First, the

definition of remission was based only on two independent time-points (6 OR 12 months) and used to predict radiographic progression over the following year. Although this was also the methodology used by the ACR/EULAR group,[4] it is recognized that alternative ways exist to quantify sustained remission, which might be useful both in understanding the construct of remission and investigating its relationship with structural damage accrual.[33] Second, good outcome was assessed only within the second year after randomization. Although this is the efficacy endpoint used in most trials, longer follow-up assessment could provide different results.[34] Third, data from clinical trials may not accurately reflect clinical practice due to selection bias, related to comorbidities and disease duration, among other factors. However, we would expect that PGA's relationship with disease activity would become worse with disease duration and associated increase in comorbidity and structural damage. Some changes to the published protocol for this study need to be disclosed, namely the use of ΔmTSS≤0.5 units as the primary outcome instead of the ≤0 cut-off, for the reasons outlined in the methods section. For clarity, we do not describe results with the ≤3 ΔmTSS, as it brought no additional information (data not shown).

The most relevant implications of this study for clinical practice and research relate to the most appropriate definition of remission and its use as the guiding target for therapy. Our results demonstrate that patients in PGA-near-remission do not differ significantly from those in 4V-remission in terms of radiographic damage accrual, while they can be clearly separated from those in non-remission. This supports the aggregation of the first two groups, i.e. the proposed 3V-remission definition. Contrary to ACR/EULAR [4], but in line with previous initial evidence,[13, 21] our results demonstrated that the 3V-remission definition does not significantly diminish the ability to predict structural damage, while it may significantly reduce the risk of overtreatment, if not achieving 4v remission prompts therapy escalation.[19, 20]

The ACR/EULAR committee also addressed the 3V-definition and reached the opposite conclusion.[4] This may be explained by differences in methodology and reasoning. First, ACR/EULAR tested one single and very strict cut-off to define good radiographic outcome (ΔmTSS≤0), which is, in our view, excessively stringent, as it does not even allow for a

difference of one unit in change score in the total of 448 joints assessed by the 2 radiograph assessors, which is averaged to 0.5. In our study, using ΔmTSS≤0 abrogated all differences in the proportion of GRO between 4v-remission and PGA-near-remission, although the predictive accuracy was still higher with the 3v than with the 4v definition of remission. Second, the ACR/EULAR committee limited their analysis to 4V vs 3V, which significantly overlap, thus "diluting" the characteristics of a very unique group of patients: PGA-near-remission. Also, the number of patients analysed by ACR/EULAR was much lower. Another issue, the decision of the ACR/EULAR committee was, seemingly, strongly influenced by the much better prediction of good functional and "overall" good outcomes for the 4V- versus the 3V-remission. We believe that this is flawed by collinearity and circularity, because PGA is so closely related to function.[9, 14, 17] PGA is bound to predict HAQ, irrespective of disease activity and this obviously questions the use of HAQ to assess the use of PGA, especially in a definition that is intended to guide immunosuppressive therapy. Equally important is that both of these measures are largely independent from inflammation, at least in the lower levels of disease activity.[35,36] We, thus, excluded function from our analyses in this paper. Another difference: the ACR/EULAR study analysed primarily the methotrexate-alone treatment groups of three trials, while we included all arms in each of eleven trials. This may explain why our likelihood ratios of GRO between 4V-remission and non-remission are much lower than the ACR/EULAR study, given that inhibition of radiographic damage by bDMARDs has been demonstrated even in the absence of remission, thus reducing the predictive accuracy of disease activity for radiographic damage.[37-39] We believe that our approach provides a better representation of clinical practice. Finally, the selection of tools by the ACR/EULAR committee was "based (...) on the need to include patient-reported outcomes", among other factors.[4] PGA was selected because it is associated with radiographic damage.[4] While this is valid in the overall spectrum of disease activity, this argument is no longer true when the disease process is under control (SJC28, TJC28 and PCR ≤1) as demonstrated in this study and elsewhere.[17]

For patients with active disease, there is little doubt that controlling the disease is the most important means to improve the patient's condition, both at short and long-term. Once low disease activity or remission is achieved, a persistently high disease impact should become the guiding target – it needs to be analysed and understood so as to choose the best adjunctive intervention, such as analgesia, rehabilitation or anti-depressive therapy, among other pharmacological and non-pharmacological therapies.[40] PGA score is useless to this purpose - more analytic instruments, such as the Patient Reported Outcome Measurement Information System (PROMIS),[41] the RA Impact of Disease (RAID) score [42, 43] or the RA Flare Questionnaire [44] are imperative.

Overall, these results provide strong support to the proposal that the 3V definition of remission should be endorsed, and used in parallel with a separate evaluation of the patient's perspective: the dual target strategy. The first target aims at the control of inflammation (biological remission) and the other one at the control of disease impact (symptom remission), guided by clinically informative patient-reported outcome measures.[9, 16, 20] Pursuing and achieving the first is an important contribution but no guarantee that the second will be fulfilled.

Acknowledgments

We would like to acknowledge the invaluable support provided from Jos van der Velden (SAS Portugal), who assisted us with the use of SAS software and access to the SAS Clinical Trial Data Transparency Portal. We also acknowledge the support from Adam LaMana (SAS International) and from the personal from "data sharing" teams from Pfizer, AbbVie, Roche, UCB and YODA.

We also would like to acknowledge the support of Eduardo Santos (Coimbra, Portugal) in performing the meta-analyses.

Funding

This study, carried out under YODA Project #2017-1451, used data obtained from the Yale University Open Data Access Project, which has an agreement with JANSSEN RESEARCH & DEVELOPMENT, L.L.C.. The interpretation and reporting of research using this data are solely the responsibility of the authors and does not necessarily represent the official views of the Yale University Open Data Access Project or JANSSEN RESEARCH & DEVELOPMENT, L.L.C..

This study was also supported by Pfizer Inc (Project #WI225756), AbbVie Inc (Project #83303.0), and by ClinicalStudyDataRequest, which has an agreement with Roche Inc. and UCB Inc. (Project #1808). These companies provided the authors with access to the data but did not sponsor or influence this analysis. The interpretation and reporting of the results are of the exclusive responsibility of the authors.

Pedro M. Machado is supported by the National Institute for Health Research (NIHR) University College London Hospitals (UCLH) Biomedical Research Centre (BRC). The views expressed are those of the authors and not necessarily those of the (UK) National Health Service (NHS), the NIHR, or the (UK) Department of Health, or any other governmental, academic, commercial or industrial institution.

Ricardo Ferreira was supported by a grant from ARCo – Associação de Reumatologia de Coimbra, a non-profit association of health professionals.

References

1 Smolen JS, Breedveld FC, Burmester GR*, et al.* Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. *Ann Rheum Dis* 2015;75:3-15.

2 Smolen JS, Landewe R, Bijlsma J*, et al.* EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. *Ann Rheum Dis* 2017;76:960-77.

3 Singh JA, Saag KG, Bridges SL*, et al.* 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. *Arthritis Care Res* 2016;68:1-25.

4 Felson DT, Smolen JS, Wells G*, et al.* American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. *Arthritis Rheum* 2011;63:573-86.

5 van Tuyl LH, Boers M. Patient's global assessment of disease activity: what are we measuring? *Arthritis Rheum* 2012;64:2811-3.

6 Nikiphorou E, Radner H, Chatzidionysiou K*, et al.* Patient global assessment in measuring disease activity in rheumatoid arthritis: a review of the literature. *Arthritis Res Ther* 2016;18:251.

7 van Tuyl LHD, Boers M. Rheumatoid arthritis: Remission - keeping the patient experience front and centre. *Nat Rev Rheumatol* 2017;13:573-74.

8 Ferreira RJO, Duarte C, Ndosi M*, et al.* The controversy of using PGA to define remission in RA. *Nat Rev Rheumatol* 2018;14:245.

9 Ferreira RJO, Duarte C, Ndosi M*, et al.* Suppressing Inflammation in Rheumatoid Arthritis: Does Patient Global Assessment Blur the Target? A Practice-Based Call for a Paradigm Change. *Arthritis Care Res (Hoboken)* 2018;70:369-78.

10 Vermeer M, Kuper HH, van der Bijl AE*, et al.* The provisional ACR/EULAR definition of remission in RA: a comment on the patient global assessment criterion. *Rheumatology (Oxford)* 2012;51:1076-80.

11 Studenic P, Smolen JS, Aletaha D. Near misses of ACR/EULAR criteria for remission: effects of patient global assessment in Boolean and index-based definitions. *Ann Rheum Dis* 2012;71:1702-5.

12 Balogh E, Dias JM, Orr C*, et al.* Comparison of remission criteria in a tumour necrosis factor inhibitor treated rheumatoid arthritis longitudinal cohort: patient global health is a confounder. *Arthritis Res Ther* 2013;15:R221.

13 Svensson B, Andersson ML, Bala SV*, et al.* Long-term sustained remission in a cohort study of patients with rheumatoid arthritis: choice of remission criteria. *BMJ open* 2013;3:e003554.

14 Ferreira RJO, Dougados M, Kirwan J*, et al.* Drivers of patient global assessment in patients with rheumatoid arthritis who are close to remission: an analysis of 1588 patients. *Rheumatology (Oxford)* 2017;56:1573-8.

15 Gossec L, Kirwan JR, de Wit M*, et al.* Phrasing of the patient global assessment in the rheumatoid arthritis ACR/EULAR remission criteria: an analysis of 967 patients from two databases of early and

established rheumatoid arthritis patients. *Clin Rheumatol* 2018;37:1503-10.

16 Ferreira RJO, Ndosi M, de Wit M*, et al.* Dual target strategy: a proposal to mitigate the risk of overtreatment and enhance patient satisfaction in rheumatoid arthritis. *Ann Rheum Dis*. 2018/08/22 ed 2018.

17 Ferreira RJO, Carvalho PD, Ndosi M*, et al.* Impact of patient global assessment on achieving remission in patients with rheumatoid arthritis: a multinational study using the METEOR database. *Arthritis Care Res (Hoboken)* 2019; Published Online First: 2019/03/02. doi: 10.1002/acr.23866

18 Ward MM, Guthrie LC, Dasgupta A. Direct and indirect determinants of the patient global assessment in rheumatoid arthritis: Differences by level of disease activity. *Arthritis Care & Research (Hoboken)* 2017;69:323-29.

19 Landewe RBM. Overdiagnosis and overtreatment in rheumatology: a little caution is in order. *Ann Rheum Dis* 2018; Published Online First: 2018/07/06. doi: 10.1136/annrheumdis-2018-213700

20 Landewe RBM. Response to: 'Dual target strategy: a proposal to mitigate the risk of overtreatment and enhance patient satisfaction in rheumatoid arthritis' by Ferreira et al. *Ann Rheum Dis* 2018; Published Online First: 2018/08/22. doi: 10.1136/annrheumdis-2018-214221

21 Navarro-Compan V, Gherghe AM, Smolen JS*, et al.* Relationship between disease activity indices and their individual components and radiographic progression in RA: a systematic literature review. *Rheumatology (Oxford)* 2015;54:994-1007.

22 Ferreira RJO, Machado PM, Gossec L*, et al.* Long-term predictive value of including patient global assessment in Boolean remission regarding radiographic damage and physical function in patients with rheumatoid arthritis: protocol for an individual patient data meta-analysis. 2017 [Accessed date 2017 CRD42017057099]; Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017057099

23 Ferreira RJO, Welsing PMJ, Gossec L*, et al.* The impact of patient global assessment in the definition of remission as a predictor of long-term radiographic damage in patients with rheumatoid arthritis: protocol for an individual patient data meta-analysis. *Acta reumatologica portuguesa* 2018;43:52-60.

24 Arnett FC, Edworthy SM, Bloch DA*, et al.* The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;31:315-24.

25 Aletaha D, Neogi T, Silman AJ*, et al.* 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Ann Rheum Dis* 2010;69:1580-8.

26 Ory PA. Interpreting radiographic data in rheumatoid arthritis. *Ann Rheum Dis* 2003;62:597-604.

27 van der Heijde D, Schiff M, Tanaka Y*, et al.* Low rates of radiographic progression of structural joint damage over 2 years of baricitinib treatment in patients with rheumatoid arthritis. *RMD open* 2019;5:e000898.

28 Smolen JS, Pedersen R, Jones H*, et al.* Impact of flare on radiographic progression after etanercept continuation, tapering or withdrawal in patients with rheumatoid arthritis. *Rheumatology (Oxford)* 2019; Published Online First: 2019/07/02. doi: 10.1093/rheumatology/kez224

29 Fleischmann RM, Huizinga TW, Kavanaugh AF*, et al.* Efficacy of tofacitinib monotherapy in methotrexate-naive patients with early or established rheumatoid arthritis. *RMD open* 2016;2:e000262.

30 van der Heijde D, Simon L, Smolen J*, et al.* How to report radiographic data in randomized clinical trials in rheumatoid arthritis: guidelines from a roundtable discussion. *Arthritis Rheum* 2002;47:215-8.

31 Bruynesteyn K, Boers M, Kostense P*, et al.* Deciding on progression of joint damage in paired films of individual patients: smallest detectable difference or change. *Ann Rheum Dis* 2005;64:179-82.

32 Barendregt JJ, Doi SA, Lee YY*, et al.* Meta-analysis of prevalence. *J Epidemiol Community Health* 2013;67:974-8.

33 Jurgens MS, Jacobs JW, Boers M*, et al.* Alternative Ways to Quantify Sustained Remission: Applying the Continuity Rewarded Score and Patient Vector Graph. *Arthritis Care Res (Hoboken)* 2015;67:1471-4.

34 Landewe R, Ostergaard M, Keystone EC*, et al.* Analysis of integrated radiographic data from two long-term, open-label extension studies of adalimumab for the treatment of rheumatoid arthritis. *Arthritis Care Res (Hoboken)* 2015;67:180-6.

35 Welsing PM, van Gestel AM, Swinkels HL*, et al.* The relationship between disease activity, joint destruction, and functional capacity over the course of rheumatoid arthritis. *Arthritis Rheum* 2001;44:2009-17.

36 Carvalho PD, Ferreira RJO, Landewe R*, et al.* Association of seventeen definitions of remission with functional status in a large clinical practice cohort of patients with rheumatoid arthritis. *J Rheumatol* 2019; Published Online First: 2019/05/03. doi: 10.3899/jrheum.181286

37 Smolen JS, Han C, Bala M*, et al.* Evidence of radiographic benefit of treatment with infliximab plus methotrexate in rheumatoid arthritis patients who had no clinical improvement: a detailed subanalysis of data from the anti-tumor necrosis factor trial in rheumatoid arthritis with concomitant therapy study. *Arthritis Rheum* 2005;52:1020-30.

38 Smolen JS, Han C, van der Heijde DM*, et al.* Radiographic changes in rheumatoid arthritis patients attaining different disease activity states with methotrexate monotherapy and infliximab plus methotrexate: the impacts of remission and tumour necrosis factor blockade. *Ann Rheum Dis* 2009;68:823-7.

39 Landewe R, van der Heijde D, Klareskog L*, et al.* Disconnect between inflammation and joint destruction after treatment with etanercept plus methotrexate: results from the trial of etanercept and methotrexate with radiographic and patient outcomes. *Arthritis Rheum* 2006;54:3119-25.

40 Santos EJF, Duarte C, Marques A*, et al.* Effectiveness of non-pharmacological and non-surgical interventions for rheumatoid arthritis: an umbrella review. *JBI database of systematic reviews and implementation reports* 2019;17:1494-531.

41 Bartlett SJ, Orbai AM, Duncan T*, et al.* Reliability and Validity of Selected PROMIS Measures in People with Rheumatoid Arthritis. *PLoS ONE* 2015;10:e0138543.

42 Gossec L, Paternotte S, Aanerud GJ*, et al.* Finalisation and validation of the rheumatoid arthritis impact of disease score, a patient-derived composite measure of impact of rheumatoid arthritis: a EULAR initiative. *Ann Rheum Dis* 2011;70:935-42.

43 Ferreira RJO, Gossec L, Duarte C*, et al.* The Portuguese Rheumatoid Arthritis Impact of Disease (RAID) score and its measurement equivalence in three countries: validation study using Rasch Models. *Qual Life Res* 2018;27:2909-21.

44 Bartlett SJ, Barbic SP, Bykerk VP*, et al.* Content and Construct Validity, Reliability, and Responsiveness of the Rheumatoid Arthritis Flare Questionnaire: OMERACT 2016 Workshop Report. *J Rheumatol* 2017;44:1536-43.

45 Wallace BC, Dahabreh IJ, Trikalinos TA*, et al.* Closing the Gap between Methodologists and End-Users: R as a Computational Back-End. *Journal of Statistical Software* 2012;49:1-15.

46 Macaskill P, Gatsonis C, Deeks JJ*, et al.* Chapter 10 Analysing and Presenting Results. In: Deeks JJ, Bossuyt PM, Gatsonis C, eds. *Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy Version 10*: The Cochrane Collaboration; 2010.

47 Moayyedi P. Meta-analysis: Can we mix apples and oranges? *Am J Gastroenterol* 2004;99:2297-301.

48 Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539-58.

Supplementary File S1 – Statistical analyses details

Data analysis

All "primary" analyses were performed with SAS software (v.9.3), within the online secure platforms (SAS Drug Development) provided by data holders.

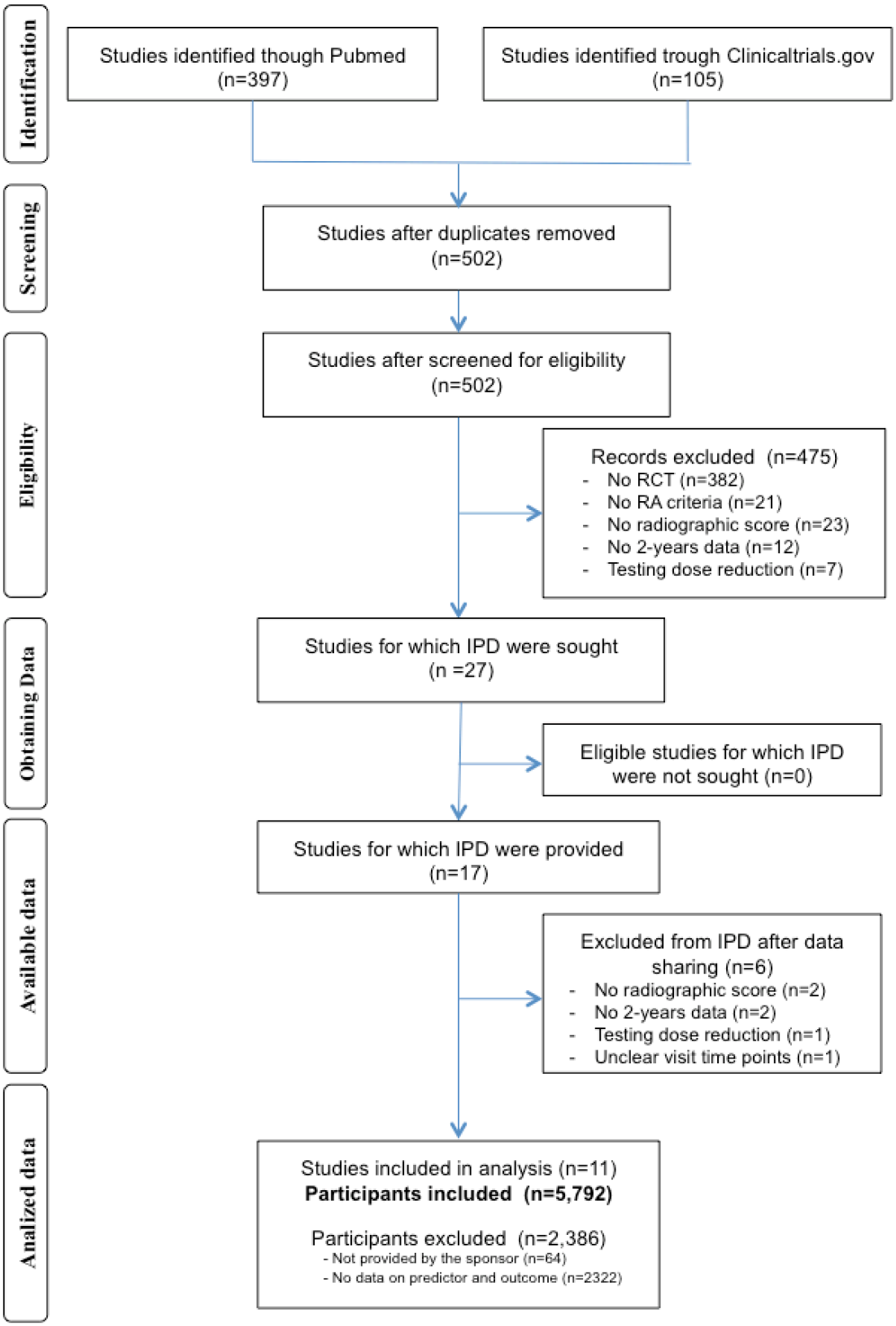
Continuous data were described as means and standard deviations (SD) and categorical data by frequencies and percentages.

The number and percentage of patients with missing values for each variable was reported per trial.

Data-synthesis

All meta-analyses except one were performed with the OpenMeta[Analyst] software,[45] using the DerSimonian-Laird random-effect method [46] and the Arcsine transformed proportion.[32] The STATA software (v.14) was used only to determine odds ratio (OR) adjusted to covariates (sensitivity analyses). The I^2 of Higgins and Thompson was calculated to quantify heterogeneity [47, 48].

Supplementary Figure S1 – Process of study identification and data access



Supplementary Table S1. Baseline characteristics of the population samples included in the studies (all placebo-controlled)

Trial name (Year of publication)	DE019 (2004)	TEMPO (2004)	COMET (2008)	RAPID 1 (2008)	RAPID 2 (2009)	GO FORWARD (2010)	GO BEFORE (2011)	LITHE (2011)	DE013 (2013)	GO FURTHER (2014)	FUNCTION (2016)
Biologic agent	Adalimumab	Etanercept	Etanercept	Certolizumab	Certolizumab	Golimumab	Golimumab	Tocilizumab	Adalimumab	Golimumab	Tocilizumab
Inclusion criteria	MTX-IR	csDMARD-IR [a]	MTX-naive	MTX-IR	MTX-IR	MTX-IR	MTX-naive	MTX-IR	MTX-naive	MTX-IR	MTX-IR
No. patients randomized	619	686	542	982	619	444	637	1196	799	592	1162
No patients available for this IPD study	619	684	542	857	582	444	637	1196	799	592	1162
No.(%) patients with predictors and outcome at 2y	425 (68.6)	442 (64.6)	344 (63.5)	650 (75.8)	417 (71.6)	352 (79.3)	499 (78.3)	796 (66.6)	540 (67.6)	483 (81.6)	844 (60.3)
Demographics											
Female (%)	75.0	76.6	73.4	82.7	81.6	80.6	82.9	83.0	74.5	81.6	79.0
Mean age (yrs)	56.0 (12.1)	52.9 (13.0)	51.5 (14.0)	52.2 (11.4)	51.6 (11.6)	50.4 (11.4)	49.5 (12.3)	52.1 (12.3)	52.0 (13.5)	51.8 (12.1)	50.0 (13.3)
Mean RA duration (yrs)	10.8 (9.1)	6.6 (5.3)	7.6 (5.4)	6.1 (4.3)	6.1 (4.1)	6.2 (6.1) [b]	2.4 (3.8) [b]	9.5 (8.0)	**0.8 (0.8)**	4.3 (4.9) [b]	**0.6 (0.6)**
RF positive (%)	84.3	66.9	97.0	82.2	76.9	83.1	82.9	78.4	84.0	90.7	86.3
Disease activity measures											
Mean DAS28CRP3v	4.9 (0.7)	5.3 (0.8)	4.9 (0.9)	5.3 (0.7)	5.3 (0.7)	4.8 (0.9)	4.8 (0.9)	4.8 (1.0)	5.3 (0.8)	5.3 (0.8)	4.7 (1.1)
Mean CRP (mg/dl)	1.8 (1.9)	2.9 (3.3)	3.6 (3.6)	2.5 (2.8)	2.4 (2.8)	1.8 (2.3)	2.5 (3.1)	2.2 (2.5)	4.0 (4.0)	2.6 (2.6)	2.2 (2.8)
Mean TJC28	14.6 (6.5)	18.2 (6.6)	14.2 /7.2)	17.8 (6.1)	17.9 (6.4)	13.5 (7.3)	14.5 (7.3)	14.8 (7.5)	16.7 (6.3)	14.9 (6.4)	14.4 (7.9)
Mean SJC28	13.1 (5.6)	15.1 (5.7)	12.2 (6.5)	14.8 (5.4)	14.4 (5.4)	9.8 (5.6)	10.7 (6.0)	11.5 (6.2)	14.3 (5.7)	10.8 (5.1)	10.6 (6.4)
Mean PGA (cm)	5.3 (2.2)	7.0 (1.7) [c]	7.6 (2.0) [c]	6.3 (1.9)	6.1 (2.0)	5.5 (2.4)	6.1 (2.3)	5.9 (2.4)	6.6 (2.3)	6.5 (1.9)	6.1 (2.4)
Mean (PhGA) (cm)	6.2 (1.7)	6.8 (1.5) [c]	6.6 (1.6) [c]	6.3 (1.5)	6.4 (1.4)	5.8 (1.7)	6.2 (1.7)	5.8 (2.1)	6.6 (1.8)	6.2 (1.6)	5.7 (2.2)
Radiographic scores [d]											
Mean baseline score	68.3 (55.2)	34.8 (48.3)	8.6 (16.8)	47.2 (56.6)	36.1 (48.7)	33.5 (47.9)	16.0 (29.1)	30.3 (30.9)	19.5 (20.5)	49.6 (55.7)	**6.1 (14.6)**

a. Other than Metrotrexate

b. missing data > 50%

c. Assessed with numeric rating scale (0 to 10) and not with visual analogue scale (0 to 10cm)

d. All trials used Sharp van der Heijde mTSS except in the LITHE trial, in which Genant mTSS was used instead.

Legend: MTX - Methotrexate, IR- Insufficient responder, IPD - Individual patient data, RA, rheumatoid arthritis, RF, Rheumatoid Factor, DAS28CRP3v, Disease Activity Score with 28-joint counts, using c-Reactive protein and 3 variables; CRP, C-Reactive Protein, TJC28, Tender 28-joint counts; SJC28, Swollen 28-joint counts; PGA, Patient Global Assessment of disease activity; PhGA, Physician Global Assessment of disease activity.

Supplementary Table S2. Pooled meta-analytic frequency of radiographic outcomes (with 95%CI) and heterogeneity statistics for each remission definition (n=5,792). This table provides complementary information to Figure 3 in the main text.

ΔmTSS cut-off	Remission Definition	% Good Outcome			I^2	% Bad Outcome			I^2
		Pooled	95%CI Lower	95%CI Higher		Pooled	95%CI Lower	95%CI Higher	
≤0.5	4V-rem.	81.1	74.4	86.9	88.6	18.9	13.1	25.6	88.6
	Non-4V-rem.	73.3	63.9	81.8	97.7	26.7	18.2	36.1	97.9
	PGA-near-rem.	78.2	69.5	85.8	90.8	21.8	14.2	30.5	90.8
	3V-rem.	79.6	72.2	86.1	94.7	20.4	13.9	27.8	94.7
	Non-3V-rem.	71.8	62.1	80.5	97.2	28.2	19.5	37.9	97.2
≤5	4V-rem.	97.5	95.4	98.9	76.2	2.5	1.1	4.6	76.2
	Non-4V-rem.	94.7	90.8	97.6	96.2	5.3	2.4	9.2	92.2
	PGA-near-rem.	96.1	92.5	98.5	85.0	3.9	1.5	7.5	85.0
	3V-rem.	96.9	94.2	98.8	90.7	3.1	1.2	5.8	90.7
	Non-3V-rem.	94.2	90.2	97.2	94.8	5.8	2.8	9.8	94.8

Legend: 4V-remission = SJC28, TJC28, CRP (in mg/dl), and PGA (0-10), all ≤1; PGA-near-remission= SJC28, TJC28, CRP (in mg/dl) ≤1 and PGA (0-10)>1; Non-remission = SJC28 >1 OR TJC28>1 OR CRP (in mg/dl)>1, irrespective of PGA value; 3V-remission= SJC28, TJC28, CRP (in mg/dl) ≤1; All definitions as observed at 6 OR 12 months. ΔmTSS = change in the modified Total Sharp Score during the second year of follow-up.

Supplementary Table S3. Meta-analyses of the adjusted[a] odds ratios to compare the predictive value of good radiographic outcomes between patients in 4V-remission and in PGA-near-remission status (at 6 OR 12 months)

Good Radiographic Outcome (from 12 to 24 months)	No. studies (participants)	4V-remission (Reference)	PGA-near-remission OR (95% CI)	I^2
ΔmTSS ≤ 0	11 (5,653)	1.00	1.06 (0.81 to 1.30)	0%
ΔmTSS ≤ 0.5	11 (5,653)	1.00	0.97 (0.69 to 1.23)	0%
ΔmTSS ≤ 5	7 (3,109)[b]	1.00	0.85 (0.02 to 2.19)	0%

a. Model adjusted to age at baseline, gender, rheumatoid factor, disease duration (except for GoBEFORE, GoFORWARD, and GoFURTHER trials as these had missing data>50%) radiographic damage at baseline, and treatment arm were included as possible confounders.

b. Without GOBEFORE, LITHE, FUNCTION, and RAPID2 trials due to invalid data obtained from logistic regressions.

Legend: 4V-remission = SJC28, TJC28, CRP (in mg/dl), and PGA (0-10), all ≤1; PGA-near-remission= SJC28, TJC28, CRP (in mg/dl) ≤1 and PGA (0-10)>1; All definitions as observed at 6 OR 12 months. ∆mTSS = change in the modified Total Sharp Score during the second year of follow-up; OR= Odds Ratio.

Supplementary Table S4. Meta-analyses of the adjusted[a] odds ratios to descriptively compare the predictive value of good outcomes between patients in 4V-remission and in 3V-remission status (6 OR 12 months)

Definition of Good Outcome (from 12 to 24 months)	No. studies (participants)	4V-remission	Non-remission	I^2	3V-remission	Non-remission	I^2
		(Reference)	OR (95% CI)		(Reference)	OR (95% CI)	
ΔmTSS ≤ 0	11 (5,653)	1.00	0.68 (0.54 to 0.84)	40%	1.00	0.73 (0.64 to 0.83)	0%
ΔmTSS ≤ 0.5	11 (5,653)	1.00	0.66 (0.50 to 0.85)	34%	1.00	0.64 (0.54 to 0.77)	0%
ΔmTSS ≤ 5	8 (3,607)[b]	1.00	0.22 (0.05 to 0.44)	0%	1.00	0.79 (0.47 to 1.12)	0%

a. adjusted analysis to: age at baseline, gender, rheumatoid factor, disease duration (except for GoBEFORE, GoFORWARD, and GoFURTHER trials as these had missing data>50%) radiographic damage at baseline, and treatment arm were included as possible confounders.

b – Without LITHE, FUNCTION, RAPID2 trials due to invalid data obtained from logistic regressions.

Legend: 4V-remission = SJC28, TJC28, CRP (in mg/dl), and PGA (0-10), all ≤1; 3V-remission= SJC28, TJC28, CRP (in mg/dl) ≤1; Non-remission = SJC28 >1 OR TJC28>1 OR CRP (in mg/dl)>1, irrespective of PGA value; All definitions as observed at 6 OR 12 months. ΔmTSS = change in the modified Total Sharp Score during the second year of follow-up; OR = Odds Ratio.

Chapter V

IMPLICATIONS FOR PATIENT CARE AND FOR NURSING

This chapter includes 1 published letter and 1 published manuscript.

Manuscript 11

Dual target strategy: a proposal to mitigate the risk of overtreatment and enhance patient satisfaction in rheumatoid arthritis.

Ferreira RJO, Ndosi M, de Wit M, Santos EJF, Duarte C,
Jacobs JWG, Machado PM, van der Heijde D, Gossec L, da Silva JAP

Ann Rheum Dis. 2018 Aug 20; doi: 10.1136/annrheumdis-2018-214199.

JOURNAL'S IMPACT FACTOR: 14.299

Number of external citations*: 1

Number of self-citations*: 1

* until 30th august 2019

Dual target strategy: a proposal to mitigate the risk of overtreatment and enhance patient satisfaction in rheumatoid arthritis

With great interest we read the viewpoint from Professor Landewé,[1] calling for more caution, research and debate regarding the risks of overdiagnosis and overtreatment in rheumatology. Strongly agreeing with the overall message, especially that '(…) overtreatment is hardly discussed but likely present', we would like to contribute to this discussion by raising an issue that touches base on two paradigms listed by Professor Landewé: remission and evidence-based rheumatology.

There is now ample evidence that a substantial proportion (12%–38%) of patients with rheumatoid arthritis (RA) do not achieve the status of remission according to disease activity indices, solely because of a patient global assessment (PGA) score >1 (0–10 scale, 10=worst).[2 3] If the elevated score on PGA does not reflect disease activity, additional immunosuppressive agents cannot improve the status of these patients, as inflammation is already essentially abrogated. Elevated PGA, therefore, may induce the risk of overtreatment when applying disease indices or Boolean-based criteria to define the treatment aim, which is remission or at least low disease activity (LDA) according to current treatment recommendations.[4 5] Naturally, patients who still report relevant disease symptoms despite the absence of significant inflammation need to be appropriately assessed and supported to address disease impact, but this probably calls for adjuvant interventions, rather than reinforcement of immunosuppressive therapy.[6 7]

This has led to our recent proposal that the management of RA should be guided by a dual treat-to-target strategy (dual T2T): one representing the control of inflammation (biological remission) and the other the control of disease impact (symptom remission).[8] Remission of inflammation often also results in symptom remission, but not always.[2 8]

Given that the relationship between PGA and disease activity is not consistent, especially around the cut-offs of disease activity indices for LDA and remission,[8] it is proposed that the definition of biological remission should not include PGA, but that it should be defined by the number of swollen and tender joints and C-reactive protein, that is, the three-variable remission. This proposition is further supported by the evidence that, overall, PGA is driven by multiple factors beyond inflammation,[9 10] including non-inflammatory pain, limitation in physical function, fatigue, depression and comorbidities,[2 8] as well as by socioeconomic and cultural factors.[11] Recent research has demonstrated that patients vary enormously in their interpretation of the question and as many as 40% of them find scoring of PGA confusing.[12 13] This is accrued by the existence of several different formulations of PGA, which, in itself, may influence the remission rate in 4.7%–6.3%.[14]

Symptom remission, an important outcome from the patient's perspective,[15 16] would, in this proposal, be served better by an instrument capable of measuring and discriminating the underlying causes of ongoing disease impact, so as to guide the selection of appropriate interventions. Currently, the best-suited instrument for this purpose seems to be the Rheumatoid Arthritis Impact of Disease (RAID) score[17 18] with its seven domains, individually considered adequate to guide treatment decisions.[18] Whatever the instrument chosen, treatment decisions must always be based on two-way communication and shared decision-making between the patient and the caring team.[19]

We believe that this novel strategy, that is, dual T2T and the use of the three-variable remission and RAID, would significantly reduce the risk of overtreatment. Step-up of treatment strategies according to recommendations would still be used until biological remission is achieved. If, at this stage, symptom remission is not achieved, adjuvant therapy may be considered, according to the most affected domains of impact according to RAID. Actually, these domains of impact should be considered from the beginning, because patient well-being is a core objective of treatment and because some of them, for example, depression, may actually diminish the probability of achieving the biological target.[20]

It has been argued that 'the remission criteria are designed for research and for optimum specificity, and not for use in treat-to-target schemes',[21] but this does not preclude their frequent use in clinical settings. It has also been put forward that 'most rheumatologists in practice do not need new instruments to decide which patients are most likely have residual disease and are in need of switching their treatment as opposed to patients with comorbidities that confound the interpretation of their RA symptoms'.[22] Professor Landewé argues,[1] conversely, that 'sometimes (…) guidelines are too rigidly pursued by clinicians who may ignore the needs of individual patients'. In fact, the European League Against Rheumatism recommendations for the management of RA state that treatment must be based on a shared decision with patients and that decisions on immunosuppressive treatment should take structural damage, comorbidities or contraindications into account.[4] The risk of overtreatment would be further diminished if recommendations specifically address major aspects that may 'confound' the practising rheumatologist.

We believe that the proposal presented herein represents an important step forward in this direction. It also highlights the need to keep the patient's perspective and needs at the bull's eye of the treatment target, underlining the importance of a holistic approach to patient assessment and treatment, in order to achieve optimal results.[19] In clinical trials, the improved relationship between the three-variable disease index/remission criteria and disease activity would result in a more accurate determination of the actual efficacy and value of disease-modifying medications.

Additional evidence is needed to fully support this paradigm shift, namely by investigating whether exclusion of PGA negatively affects the relationship between remission and structural damage progression—the crunch of the matter, after all. Work is under way.[23]

Ricardo J O Ferreira,[1,2] Mwidimi Ndosi,[3,4] Maarten de Wit,[5,6] Eduardo José Ferreira Santos,[1,2,7] Cátia Duarte,[1,8] Johannes W G Jacobs,[9] Pedro M Machado,[10,11] Désirée van der Heijde,[12] Laure Gossec,[13,14] Jose A P da Silva[1,8]

[1]Rheumatology Department, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal
[2]Health Sciences Research Unit: Nursing (UICiSA:E), Nursing School of Coimbra (ESEnfC), Coimbra, Portugal
[3]Department of Nursing and Midwifery, University of the West of England, Bristol, UK
[4]Academic Rheumatology Unit, University Hospitals Bristol, Bristol, UK
[5]Patient Research Partner, EULAR Standing Committee of People with Arthritis/Rheumatism in Europe (PARE), Zurich, Switzerland
[6]Department of Medical Humanities, Amsterdam University Medical Center, Amsterdam Public Health (APH), Amsterdam, The Netherlands
[7]Escola Superior de Enfermagem do Porto, Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto, Porto, Portugal
[8]Coimbra Institute for Clinical and Biomedical Research (iCBR), Faculty of Medicine, University of Coimbra, Coimbra, Portugal
[9]Department of Rheumatology and Clinical Immunology, University Medical Center, Utrecht, The Netherlands

[10]Centre for Rheumatology and MRC Centre for Neuromuscular Diseases, University College London, London, UK
[11]Rheumatology Department, Northwick Park Hospital, London North West University Healthcare NHS Trust, London, UK
[12]Rheumatology Department, Leiden University Medical Center, Leiden, The Netherlands
[13]Sorbonne Universités, UPMC University Paris 06, Institut Pierre Louis d'Epidémiologie et de Santé Publique, GRC-UPMC 08 (EEMOIS), Paris, France
[14]Rheumatology Department, AP–HP, Pitié-Salpetrière Hospital, Paris, France

Correspondence to Dr Ricardo J O Ferreira, Rheumatology Department, Centro Hospitalar e Universitário de Coimbra, Coimbra 3000-075, Portugal; rferreira@reumahuc.org

Handling editor Josef Smolen

Contributors RJOF and JAPdS wrote the draft of the manuscript and all coauthors revised it. The final version was approved by all coauthors.

Competing interests None declared.

Patient consent Not required.

Provenance and peer review Not commissioned; internally peer reviewed.

To cite Ferreira RJO, Ndosi M, de Wit M, *et al*. *Ann Rheum Dis* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/annrheumdis-2018-214199

Received 28 July 2018
Accepted 31 July 2018

► http://dx.doi.org/10.1136/annrheumdis-2018-214221

Ann Rheum Dis 2018;**0**:1–2. doi:10.1136/annrheumdis-2018-214199

REFERENCES

1 Landewé RBM. Overdiagnosis and overtreatment in rheumatology: a little caution is in order. *Ann Rheum Dis* 2018:annrheumdis-2018-213700.
2 Ferreira RJO, Dougados M, Kirwan JR, *et al*. Drivers of patient global assessment in patients with rheumatoid arthritis who are close to remission: an analysis of 1588 patients. *Rheumatology* 2017;56:1573–8.
3 Ferreira R, Ndosi M, Duarte C, *et al*. Influence of patient global assessment on the disease activity assessment in patients with rheumatoid arthritis: a meteor cross-sectional study [Abstract]. *Ann Rheum Dis* 2017;76(Suppl 2):1510–10.
4 Smolen JS, Landewe R, Bijlsma J, *et al*. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. *Ann Rheum Dis* 2017 [76 960 77].
5 Smolen JS, Breedveld FC, Burmester GR, *et al*. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. *Ann Rheum Dis* 2016;75:3–15.
6 de Hair MJH, Jacobs JWG, Schoneveld JLM, *et al*. Difficult-to-treat rheumatoid arthritis: an area of unmet clinical need. *Rheumatology* 2017. [Epub ahead of print 04 Oct 2017].
7 Santos EJF, Duarte C, Ferreira RJO, *et al*. Determinants of happiness and quality of life in patients with rheumatoid arthritis: a structural equation modelling approach. *Ann Rheum Dis* 2018;77:1118–24.
8 Ferreira RJO, Duarte C, Ndosi M, *et al*. Suppressing Inflammation in Rheumatoid Arthritis: Does Patient Global Assessment Blur the Target? A Practice-Based Call for a Paradigm Change. *Arthritis Care Res* 2018;70:369–78.
9 Nikiphorou E, Radner H, Chatzidionysiou K, *et al*. Patient global assessment in measuring disease activity in rheumatoid arthritis: a review of the literature. *Arthritis Res Ther* 2016;18:251.
10 Jacobs JW, Ten Cate DF, van Laar JM. Monitoring of rheumatoid arthritis disease activity in individual patients: still a hurdle when implementing the treat-to-target principle in daily clinical practice. *Rheumatology* 2015;54:959–61.
11 Putrik P, Ramiro S, Hifinger M, *et al*. In wealthier countries, patients perceive worse impact of the disease although they have lower objectively assessed disease activity: results from the cross-sectional COMORA study. *Ann Rheum Dis* 2016;75:715–20.
12 Henriques M, Duarte C, Ndosi M, *et al*. "It can't be zero": a qualitative study of patients' perspective on patient global assessment in rheumatoid arthritis [abstract]. *Ann Rheum Dis* 2017;76(Suppl 2):112.
13 Hirsh J, Wood P, Keniston A, *et al*. Limited health literacy predicts patient confusion about patient global assessments of disease activity and rheumatoid arthritis model disease states. *Arthritis Care Res* 2018 [Epub ahead of print 29 Jun 2018].
14 Ferreira RJO, Eugénio G, Ndosi M, *et al*. Influence of the different "patient global assessment" formulations on disease activity score by different indices in rheumatoid arthritis. *Clin Rheumatol* 2018;37:1963–9.
15 van Tuyl LH, Hewlett S, Sadlonova M, *et al*. The patient perspective on remission in rheumatoid arthritis: 'You've got limits, but you're back to being you again'. *Ann Rheum Dis* 2015;74:1004–10.
16 Acebes C, Andreu JL, Balsa A, *et al*. Exploring the remission concept in rheumatoid arthritis with patients and rheumatologists: time for a new approach? *Clin Exp Rheumatol* 2017;35:816–22.
17 Gossec L, Paternotte S, Aanerud GJ, *et al*. Finalisation and validation of the rheumatoid arthritis impact of disease score, a patient-derived composite measure of impact of rheumatoid arthritis: a EULAR initiative. *Ann Rheum Dis* 2011;70:935–42.
18 Ferreira RJO, Gossec L, Duarte C, *et al*. The Portuguese Rheumatoid Arthritis Impact of Disease (RAID) score and its measurement equivalence in three countries: validation study using Rasch Models. *Quality of Life Research* 2018 [Epub ahead of print 01 Aug 2018]
19 Kiely PDW, Nikiphorou E. Management of rheumatoid arthritis. *Medicine* 2018;46:216–21.
20 Matcham F, Davies R, Hotopf M, *et al*. The relationship between depression and biologic treatment response in rheumatoid arthritis: an analysis of the British Society for Rheumatology Biologics Register. *Rheumatology* 2018;57:835–43.
21 van Tuyl LHD, Boers M. The controversy of using PGA to define remission in RA. *Nat Rev Rheumatol* 2018;14:245.
22 van Tuyl LHD, Boers M. Rheumatoid arthritis: remission - keeping the patient experience front and centre. *Nat Rev Rheumatol* 2017;13:573–4.
23 Ferreira RJO, Welsing PMJ, Gossec L, *et al*. The impact of patient global assessment in the definition of remission as a predictor of long-term radiographic damage in patients with rheumatoid arthritis: protocol for an individual patient data meta-analysis. *Acta Reumatol Port* 2018;43:52–60.

Manuscript 12

Shared-decision making in people with chronic disease: Integrating the biological, social and lived experiences is a key responsibility of nurses

Ferreira RJO*, Santos EJF*, de Wit M, Marques A, Barbiéri-Figueiredo MC, Marques A, Ventura F, da Silva JAP**, Ndosi M**

Musculoskeletal Care 2019, doi: 10.1002/msk.1443.

Received: 10 October 2019 | Revised: 22 October 2019 | Accepted: 23 October 2019

DOI: 10.1002/msc.1443

SHORT REPORT

WILEY

Shared decision-making in people with chronic disease: Integrating the biological, social and lived experiences is a key responsibility of nurses

Ricardo J.O. Ferreira[1,2†] | Eduardo J.F. Santos[1,2,3†] | Maarten de Wit[4,5] | Andréa Marques[1,2,6] | Maria do Céu Barbieri-Figueiredo[3,7,8] | António Marques[2,9] | Filipa Ventura[2] | José A.P. da Silva[1,10‡] | Mwidimi Ndosi[11‡]

[1]Rheumatology Department, Centro Hospitalar e Universitário de Coimbra (CHUC), Coimbra, Portugal

[2]Health Sciences Research Unit: Nursing (UICISA: E), Nursing School of Coimbra (ESEnfC), Coimbra, Portugal

[3]Abel Salazar Institute of Biomedical Sciences, University of Porto, Porto, Portugal

[4]Patient research partner, EULAR Standing Committee of People with Arthritis/Rheumatism in Europe, Zurich, Switzerland

[5]Department of Medical Humanities, Amsterdam University Medical Centre, Amsterdam, The Netherlands

[6]Nursing School of Coimbra, Coimbra, Portugal

[7]Nursing School of Porto, Porto, Portugal

[8]CINTESIS – Center for Health Technology and Services Research, University of Porto, Porto, Portugal

[9]AGI médica I, Centro Hospitalar e Universitário de Coimbra (CHUC), Coimbra, Portugal

[10]Coimbra Institute for Clinical and Biomedical Research (iCBR) – Faculty of Medicine, University of Coimbra, Coimbra, Portugal

[11]Department of Nursing and Midwifery, University of the West of England, Bristol, UK

Correspondence
Ricardo J. O. Ferreira, Rheumatology Department – Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal.
Email: rferreira@reumahuc.org

KEYWORDS: Nursing, Communication, Rheumatoid Arthritis

1 | INTRODUCTION

Shared decision-making (SDM) is a collaborative process through which patients and their providers make healthcare decisions together, based on the best scientific evidence available and the health professional's experience, as well as the patient's values and preferences (Chewning et al., 2012). This key feature of person-centred care is advocated widely as being crucial for successful disease management in chronic diseases (de Wit, 2017; Ekman et al., 2011; McCormack et al., 2015; Voshaar, Nota, van de Laar, & van den Bemt, 2015). Despite this, its implementation continues to be delayed.

When making decisions on their own health, patients value not only clinical/biological outcomes, but also, and often to a greater extent, the way they feel the disease affects their life. The trend to capture patient perspectives using patient-reported outcome measures (PROMs), as an attempt to serve person-centred care, is still growing (Fautrel et al., 2018; Harding, Wait, & Scrutton, 2015). However, when it comes to treatment decisions in real-world practice, the primary target is defined by the physician in charge and is often limited to the biological process of the disease. Patients' personal goals come into management plans only when the medical treatment seems to fail or, in the best of circumstances, they are considered for adjunctive treatment options.

Nursing is characterized by evidence-based practice and SDM with the patient, and takes place in the context of a multidisciplinary team care (Bech et al., 2019). Therefore, nurses should have a pivotal role in assessing and managing the impact of disease and promoting SDM (Bala et al., 2018; Salisbury et al., 2018; Ventura, 2016).

This article discusses how nurses can contribute to patient-centred care in chronic diseases through the use of PROMs and coordination of the patient's representation in treatment decisions. Inspired by data from observational studies we have recently conducted with patients with rheumatoid arthritis (RA), an archetype of

[†]Joint first authors

[‡]Joint last authors

many chronic diseases (Shaul, 2010), we propose a strategy to address clinical treatment targets and personal goals in chronic diseases using SDM in the multi-professional team context.

2 | DISEASE CONTROL IS NOT EQUIVALENT TO ABROGATION OF DISEASE IMPACT

Many chronic conditions, such as rheumatic diseases, are characterized by a deregulated immune system that primarily affects a specific organ (Chen et al., 2017; Schultze & Rosenstiel, 2018) and can severely affect all areas of life, including physical, social and psychological well-being (Santos, Duarte, et al., 2018; Taylor, Moore, Vasilescu, Alvir, & Tarallo, 2016). Developments in pharmacological treatments over the last two decades have revolutionized the management of many of these conditions, effectively reducing the inflammatory process and keeping it low or in remission. It has also reduced the risk for complications associated with chronic inflammation (Dinarello, 2010; Kiely & Nikiphorou, 2018).

Paradoxically, these unprecedented pharmacological developments are not always mirrored by patients' overall perception of well-being (Fautrel et al., 2018; Gruffydd-Jones, 2019; Taylor et al., 2016; Torres-González et al., 2014). Control of the disease process does not necessarily mean control of the impact that the disease (and its treatment) has on patients' lives. To maximize long-term outcomes and quality of life (QoL), people with chronic diseases need to develop self-management skills and the ability to manage the symptoms and treatment regimes, and learn to deal with the physical and psychosocial consequences as well as the lifestyle changes inherent to living with a chronic condition (Barlow, Wright, Sheasby, Turner, & Hainsworth, 2002; Huber et al., 2011).

Our recent research has highlighted that each patient has a unique perception of his/her disease (Santos, Duarte, et al., 2018). Personality traits have a considerable influence on the perception of the disruption caused by the disease, with decisive consequences on QoL and happiness (Santos, Duarte, et al., 2018). Accordingly, treatment strategies focusing solely on the control of the disease process have a limited effect on disease symptoms and QoL, and probably a minor effect on happiness (Ferreira et al., 2017, Ferreira, Carvalho, et al., 2019; Santos, Duarte, et al., 2018; Santos et al., 2019a; Silva, Duarte, Ferreira, Santos, & da Silva, 2019). To grasp fully the dimensions affected by the disease and the psychosocial context, a more holistic assessment of patients is needed as a basis for subsequent interventions that go beyond pharmacological treatment and control of the pathological process (Santos, Duarte, et al., 2019). Patients and society have rising expectations of healthcare, and their perspectives and priorities need to be adequately and sufficiently considered—that is, incorporated into management decisions. This can be achieved in clinical care through the use of validated PROMs (Weldring & Smith, 2013). In order to maximize the benefit of PROMs in clinical practice, the targeted domains (disease process, disease impact or personal goals) need to be clear and relevant, to both patient and health professional.

3 | INCLUSION OF PROMS MAY CHALLENGE THE TREATMENT TARGET(S)

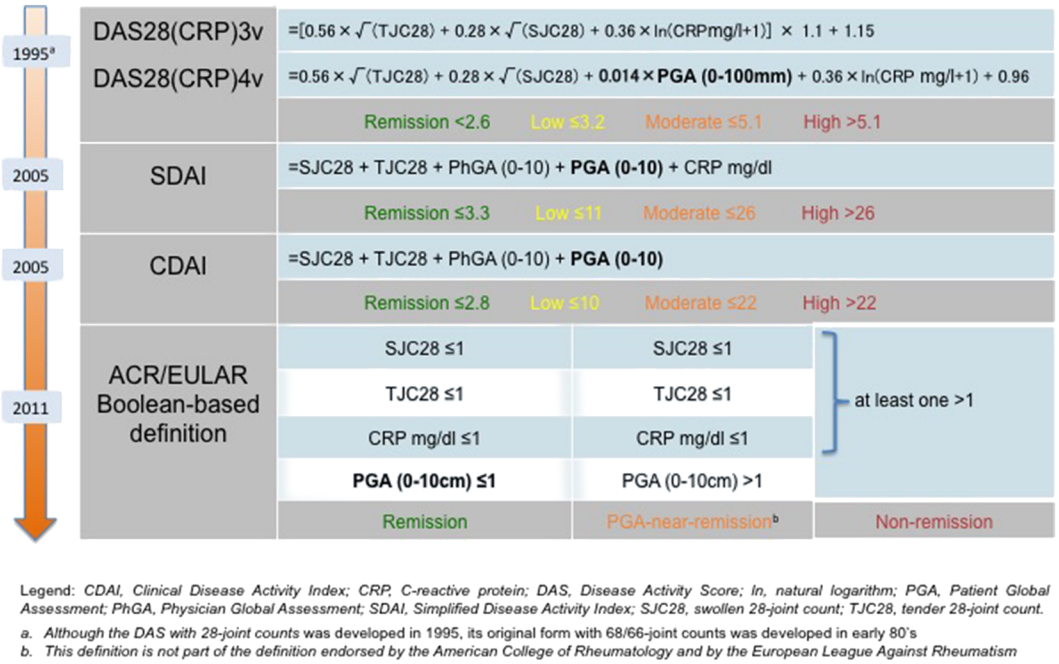
In rheumatology, and specifically in RA, two international consortia achieved consensus regarding the need to collect PROMs regularly in addition to objective or physician-reported outcomes. The first initiative, by the American College of Rheumatology, recommended a core set of patient-reported measures such as pain, physical function and patient global assessment of disease activity (PGA) to be used in clinical trials. The PGA comprises a single question, assessing the patient perception of disease/arthritis activity on a 0 to 100 mm visual analogue scale (VAS). These measures were meant to complement the standard medical assessments such as tender and swollen joint counts, acute phase reactants and the physician global assessment of disease activity (Castrejon & Pincus, 2012; Felson et al., 1993). In the composite measure of disease activity (Disease Activity Score in 28 joints [DAS28]), PGA represents, at most, 1.4 out of the maximum score of 9.4 points (Anderson, Zimmerman, Caplan, & Michaud, 2011). This means that, although included, the patient's perspective has a minimal influence (Figure 1).

The second consortium mandated the inclusion of PGA in the definitions of remission used as targets of immunosuppressive therapy (Felson et al., 2011). This decision signified an important step towards patient involvement in treatment decisions (van Tuyl et al., 2011). The importance of PGA in these tools has increased substantially over time: from a nearly irrelevant weight, to having the same impact in the final score as the clinical components. Using the Boolean-based definition of remission, a patient with no overt signs of inflammation (a score of zero on all clinical measures) is considered to fail remission if the PGA score is >1 (see Figure 1).

Studying the group of patients with RA who have no overt signs of inflammation but fail remission solely because of having a PGA >1/10 (PGA near-remission or near-misses) has become of great interest. The question is, then: "How can we understand and overcome this paradox, where we see patients whose disease process is under control but still report substantial disease impact on their daily life?" Our research tested two main hypotheses: (1) the integration of PGA in tools to define remission blurs the treatment target; and (2) the patient's needs and goals should be addressed through separate management targets.

First, we demonstrated that there were almost twice as many patients in PGA-near-remission status as those in "full" remission in an international cohort (Ferreira, Carvalho, et al., 2019), and up to 37% of all patients in some settings (Ferreira, Duarte, et al., 2018). Among these PGA-near-remission patients, about one-third scored a PGA >4/10 (Ferreira, Carvalho, et al., 2019). This demonstrates that, despite having no measurable signs of inflammation, many patients perceive considerable disease impact. Understanding the reasons driving the high PGA in the absence of active disease is, therefore, essential in order to address the causes with appropriate interventions (other than immunosuppressive agents).

Second, following focus group interviews, we showed that differences in terminology ("arthritis", "disease", "health"), time references



Legend: *CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; DAS, Disease Activity Score; ln, natural logarithm; PGA, Patient Global Assessment; PhGA, Physician Global Assessment; SDAI, Simplified Disease Activity Index; SJC28, swollen 28-joint count; TJC28, tender 28-joint count.*

a. *Although the DAS with 28-joint counts* was developed in 1995, its original form with 68/66-joint counts was developed in early 80's
b. *This definition is not part of the definition endorsed by the American College of Rheumatology and by the European League Against Rheumatism*

FIGURE 1 The growing importance of PGA in different treatment decision algorithms used in rheumatoid arthritis (RA). This figure shows the components and scoring algorithms of four disease activity tools currently in use in clinical practice, and in clinical trials in RA. They are presented in chronologic order of development. ACR: American College of Rheumatology; CDAI: Clinical Disease Activity Index; CRP: C-reactive protein; DAS: Disease Activity Score; EULAR: European League Against Rheumatism; ln: natural logarithm; PGA: Patient Global Assessment; PhGA: Physician Global Assessment; SDAI: Simplified Disease Activity Index; SJC28: swollen 28-joint count; TJC28: tender 28-joint count[a]Although the DAS with 28-joint counts was developed in 1995, its original form with 68/66-joint counts was developed in early 1980s [b]This is not part of the definition endorsed by the ACR and by EULAR. Figures in bold show the growing importance of PGA in these tools. The DAS28 has two forms: one does not include PGA, and the other attributed to PGA a total of 1.4 (=0.014*100) out of a maximum score of 9.4 points (Anderson et al., 2011). In the SDAI and CDAI tools, if the PGA is 4 and all other components are (near) zero, it is impossible to be classified as in remission. In the Boolean-based remission, even a score of 1.1 in the PGA will preclude patients from being in remission.

("last week", "today", no reference) and scales ("0 to 10", or "0–10 cm") used in current PGA formulations make these open to different interpretation by patients, and influence their responses (Ferreira, de Wit, et al., 2019). Most patients are also unaware of the purpose of PGA, and have difficulties in completing the measurements reliably (Ferreira, de Wit, et al., 2019). With a quantitative study, we were able to confirm that the use of different versions of PGA introduces systematic errors in the rate of remission (Ferreira, Eugenio, et al., 2018).

Finally, we showed that PGA from patients in near-remission is not associated with disease activity but rather with fatigue, pain, anxiety, depression, physical well-being and functional limitations (Ferreira et al., 2017; Ferreira, Duarte, et al., 2018, Ferreira, Carvalho, et al., 2019).

In summary, PGA, a PROM that is commonly used in RA, raises a number of concerns regarding its validity, not only due to the inconsistencies in its formulations, but especially because it has little relationship with the domain it is supposed to represent: disease activity. Additionally, owing to its inclusion in treatment decision algorithms (Figure 1), some clinicians may disregard other domains of interest to patients. A more comprehensive assessment of the patient perspective, necessarily meaningful to the person, is needed in order to provide guidance for the selection of adjunctive measures (addressing fatigue, depression or pain) in the context a multiprofessional management team.

The above-mentioned considerations, derived from studies in RA, are naturally adaptable to a variety of chronic diseases, given that, in all conditions, clinical and personal targets should exist and coexist. Inflammatory bowel and neurological diseases are two examples of the increasing tendency to adopt a treat-to-target strategy in different fields (Agrawal & Colombel, 2019; Jacobs, Giovannoni, & Schmierer, 2018).

4 | TO BE USEFUL IN PRACTICE, PROMS NEED TO BE VALID AND MEANINGFUL

The use of PROMs, initially established in clinical trials, is increasingly getting recognition by regulators, clinicians and patients (Gossec, Dougados, & Dixon, 2015). However, their implementation in clinical practice has not been easy (Ganesan, 2018; Nelson et al., 2015). One of the main barriers to its implementation lies in the willingness of healthcare professionals, who already have high workloads, to focus on individual needs and perceptions of disease impact, in addition to disease activity measures (Fautrel et al., 2018). Clinical consultations are short, and it may be difficult to determine and interpret PROM scores in order to make clinical decisions in accordance (Ganesan, 2018; Porter et al., 2016; Talib et al., 2018). Patients value PROMs

but these can only improve care if clinicians prioritize and use them (Talib et al., 2018). The combination of PROMs with innovative technologies, such as mobile devices, apps and computer-adaptive tests, creates new opportunities for patients and health professionals. However, further research and consensus are needed (Basch, Barbera, Kerrigan, & Velikova, 2018; Fautrel et al., 2018; Porter et al., 2016).

Another concern is that commonly structured questionnaires, with closed questions, give insufficient opportunity for patients to express their personal views and needs (Philpot et al., 2018).

Patient input throughout all development stages of PROMs is of paramount importance, in order to ensure meaningfulness from the patient's point of view (Ferreira, Gossec, et al., 2018; Ferreira, de Wit, et al., 2019). Such a development process requires robust methodological procedures for the construction and validation of PROMs (Boers et al., 2014). Some examples of instrument development that follow the golden standard of patient involvement are the elaboration of the "Bristol RA Fatigue" (BRAF) scale (Nicklin, Cramp, Kirwan, Urban, & Hewlett, 2010) and the Psoriatic/Rheumatoid Arthritis Impact of Disease (PsAID/RAID) score (de Wit, Kvien, & Gossec, 2015; Gossec et al., 2009). The robust methodology ensures enhanced specificity, sensibility and overall psychometric properties, when compared with other, less robustly developed tools (Santos, Duarte, da Silva, et al., 2019).

PROMs need to be reliable, transculturally valid and meaningful to patients and health professionals (Santos, Duarte, da Silva, et al., 2019). Moreover, in clinical practice, patients should be instructed on the purpose of the measurements, and also on using them proactively to discuss the treatment plan with the multidisciplinary team (Ferreira et al., 2019b).

5 | THE DUAL TARGET STRATEGY: CLINICAL TREATMENT TARGETS AND PERSONAL GOALS

In the face of the above evidence, our research group, composed of patient research partners, nurses, psychologists and rheumatologists, proposes an ambitious approach and a paradigm shift: the dual target strategy. According to this paradigm, remission of the disease process (biological remission) should be considered in parallel with the target of remitting impact (patient's remission). Achieving this would require a highly coordinated multi-professional team, with all its healthcare members working toward shared goals and managing both targets. In such circumstances, the physician may continue to focus on the first target while the other healthcare members, led by the nurse, ensure that both targets are met (Ferreira, Ndosi, de Wit, et al., 2018). This may represent a structural change in the organization of care in countries where nurses do not have extended roles (Bech et al., 2019). We seek to ensure that reaching the patient's remission is considered of equal value as biological remission as a hallmark of high-quality person-centred care. This requires the multidisciplinary team to assess and manage the holistic impact of the disease on the patient, placing his/her needs at the centre of the decision-making process (van Tuyl & Boers, 2017).

Figure 2 presents our proposed model, combining subjective and objective outcomes guiding shared decision within a dual-target approach: personal goals and clinical treatment targets. The first should ideally be guided and measured by personalized PROMs, while the latter by clinical measures. For the purpose of illustration, we present a fictitious case study in Box 1.

Box 1. **Fictitious case study on dual-target strategy**

Maria is a 35-year-old mother who experienced a flare of RA after giving birth to a healthy boy. She is currently struggling to manage hand joint pain and fatigue. These symptoms strongly affect her capacity to hold and care for the baby, as well as returning to work. Informed discussions take place regarding the reintroduction of an immunosuppressive agent to the detriment of breastfeeding. Clinical targets are established, to reach during the following month: (i) the disease activity would be reduced from a DAS28–C-reactive protein (3v) = 4.9 to ≤3.2, and (ii) joint pain VAS from 7 to 3 following adjustment of analgesics and education on how to maximize their effect. Personal goals are also established—namely, reducing fatigue from 9 to 5, facilitated by readjustment of daily activities and planning time to rest, with the cooperation of her husband. Moreover, the nurse discusses with Maria alternative strategies to reinforce the attachment to her son, so highly valued by Maria, including the use of a baby sling whenever possible, and daily skin-to-skin contact moments. Here, both Maria's satisfaction and attachment can be measured with adequate PROMs.

A preliminary study has explored the need for a dual-target strategy in the management of RA (n = 101) by determining the proportion of patients who achieved biological remission (using the Clinical Disease Activity Index [CDAI]) and individual patient treatment goals (using the Goal Attainment Scale) (Turner-Stokes, 2009). After 3–5 months of follow-up, 44% of patients achieved both targets, while 22% achieved only personal goals and not the CDAI target, and 18% achieved the opposite scenario (Oppenauer et al., 2019). Further research is needed to test the feasibility and (long-term) effectiveness of this model in rheumatology and other areas of care. Few other instruments exist that allow patients to define their priorities, such as the Patient Goal Priority Questionnaire (PGPQ) and Patient Goal Priority List (PGPL) (Asenlof & Siljeback, 2009), which have been used in physical therapy treatment. These tools start by asking individuals to list their everyday life activities affected by pain, and rank their priority in their lives, assessing also other concepts, such as frequency of the activity, satisfaction, self-efficacy, fear of behaviour performance, readiness to adopt new behaviours, and expectations (Asenlof & Siljeback, 2009).

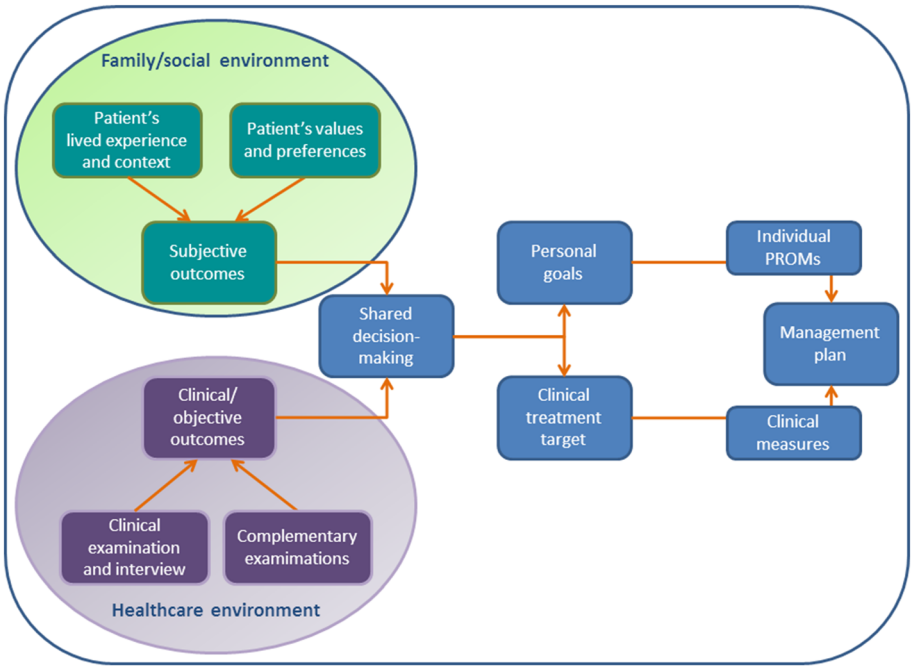


FIGURE 2 Dual-target strategy in the context of a person-centred approach

The use of individualized PROMs has different advantages, such as being responsive to the individual aspects of health-related QoL, and a higher likelihood of detecting issues that may be relevant in clinical practice. Individualized PROMs, combined with standardized clinical measures, may be effective in developing person-centred care plans, goal setting and prioritization (Porter et al., 2016). However, the establishment of the personal goals and respective intervention requires solid knowledge, experience and specific competencies from nurses, and a functional network with other health professionals. Although, in some cases, the symptoms and patient expectations may be easy to assess and monitor using PROMs (e.g., pain using the pain-VAS), other scenarios may not be that straightforward. For example, multidimensional concepts, such as QoL or the extent to which the patient's goals are achieved, may require instruction or training of the health professional, to ensure that the most appropriate PROMs are used and correctly interpreted.

6 | FINAL CONSIDERATIONS

Nurses are especially suited to champion the dual-target strategy in clinical practice for the following reasons. First, nursing is characterized by a holistic approach to care, which therefore involves incorporating patients' experiences and responses to the disease and treatments into overall patient management and within other life transitions (Meleis, 2010; Shaul, 2010). This facilitates the elicitation of preferences and priorities relevant to patients, in terms of both disease, and personal, family and social life (Meleis, 2010, 2018). Second, nurses have social and communicative competencies appropriate to facilitate warm encounters, a familial atmosphere and empathy, in addition to their professional training. This may explain the high satisfaction, security, confidence, participation, independence, self-efficacy and enhanced patient outcomes seen in nurse-led care (Bala et al., 2012; Komatsu & Yagasaki, 2014; Larsson, 2013; Sousa, Santos, Cunha, Ferreira, & Marques, 2017; Vinall-Collier, Madill, & Firth, 2016). Third, nurses are involved in the development, validation and implementation of PROMs in daily practice. They actively use PROMs to support SDM, and frequently support the patient's completion of PROMs, ensuring that they understand the measures and their possible implications in treatment decisions (Ferreira et al., 2019). Fourth, as part of the healthcare team, nurses often act as the interface (coordinator) between patients and other members of the multidisciplinary team (Bech et al., 2019). Nurses should make sure that the patient perspective is not lost during the healthcare journey—that is, the patient's personal goals are not disregarded or undervalued while pursuing clinical targets. Finally, owing to the diverse training process, entailing multiple care settings in the preregistration and postgraduate studies, nurses are in a special position to provide a first assessment in a multitude of comorbidities and clinical incidents, and to signpost the patient to the most appropriate heath professional or agency (Salisbury et al., 2018).

In conclusion, incorporating PROMs into clinical practice enhances SDM and has the potential to improve care by identifying aspects of disease impact and personal goals that are relevant to the patient but may be missed by clinical outcome measures. Careful selection of PROMs is important, to ensure that personal goals are addressed in the overall disease management. Nurses are well placed to promote appropriate use of PROMs to enhance person-centred care in chronic diseases. The feasibility of the dual-target approach, tailored to each patient, needs to be further assessed in rheumatology and in other areas of chronic disease.

ACKNOWLEDGEMENTS

We wish to thank to Professor Laure Gossec (Sorbonne Universités, UPMC University Paris 06, Paris, France) and to Professor Afaf Meleis

(University of Pennsylvania School of Nursing, Philadelphia, PA, USA) for critically revising the manuscript for its intellectual content and for their very helpful suggestions.

CONFLICTS OF INTEREST

All authors declare no conflicts of interest regarding this study.

ORCID

Ricardo J.O. Ferreira https://orcid.org/0000-0002-2517-0247
Eduardo J.F. Santos https://orcid.org/0000-0003-0557-2377
Andréa Marques https://orcid.org/0000-0002-2026-9926
Maria do Céu Barbieri-Figueiredo https://orcid.org/0000-0003-0329-0325
José A.P. da Silva https://orcid.org/0000-0002-2782-6780
Mwidimi Ndosi https://orcid.org/0000-0002-7764-3173

REFERENCES

Agrawal, M., & Colombel, J.-F. (2019). Treat-to-target in inflammatory bowel diseases, What is the target and how do we treat? *Gastrointestinal Endoscopy Clinics of North America*, *29*(3), 421–436. https://doi.org/10.1016/j.giec.2019.02.004

Anderson, J., Zimmerman, L., Caplan, L., & Michaud, K. (2011). Measures of rheumatoid arthritis disease activity: Patient (PtGA) and Provider (PrGA) Global Assessment of Disease Activity, Disease Activity Score (DAS) and Disease Activity Score with 28-Joint Counts (DAS28), Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI), Patient Activity Score (PAS) and Patient Activity Score-II (PASII), Routine Assessment of Patient Index Data (RAPID), Rheumatoid Arthritis Disease Activity Index (RADAI) and Rheumatoid Arthritis Disease Activity Index-5 (RADAI-5), Chronic Arthritis Systemic Index (CASI), Patient-Based Disease Activity Score With ESR (PDAS1) and Patient-Based Disease Activity Score without ESR (PDAS2), and Mean Overall Index for Rheumatoid Arthritis (MOI-RA). *Arthritis Care and Research*, *63*(Suppl. 11), S14–S36. https://doi.org/10.1002/acr.20621

Asenlof, P., & Siljeback, K. (2009). The Patient Goal Priority Questionnaire is moderately reproducible in people with persistent musculoskeletal pain. *Physical Therapy*, *89*(11), 1226–1234. https://doi.org/10.2522/ptj.20090030

Bala, S. V., Forslind, K., Fridlund, B., Samuelson, K., Svensson, B., & Hagell, P. (2018). Person-centred care in nurse-led outpatient rheumatology clinics: Conceptualization and initial development of a measurement instrument. *Musculoskeletal Care*, *16*(2), 287–295. https://doi.org/10.1002/msc.1233

Bala, S. V., Samuelson, K., Hagell, P., Svensson, B., Fridlund, B., & Hesselgard, K. (2012). The experience of care at nurse-led rheumatology clinics. *Musculoskeletal Care*, *10*(4), 202–211. https://doi.org/10.1002/msc.1021

Barlow, J., Wright, C., Sheasby, J., Turner, A., & Hainsworth, J. (2002). Self-management approaches for people with chronic conditions: A review. *Patient Education and Counseling*, *48*(2), 177–187. https://doi.org/10.1016/s0738-3991(02)00032-0

Basch, E., Barbera, L., Kerrigan, C. L., & Velikova, G. (2018). Implementation of patient-reported outcomes in routine medical care. *American Society of Clinical Oncology Educational Book*, *38*, 122–134. https://doi.org/10.1200/edbk_200383

Bech, B., Primdahl, J., van Tubergen, A., Voshaar, M., Zangi, H. A., Barbosa, L., … van Eijk-Hustings, Y. (2019). 2018 update of the EULAR recommendations for the role of the nurse in the management of chronic inflammatory arthritis. *Annals of the Rheumatic Diseases*, 1–8. https://doi.org/10.1136/annrheumdis-2019-215458

Boers, M., Kirwan, J. R., Wells, G., Beaton, D., Gossec, L., d'Agostino, M. A., … Tugwell, P. (2014). Developing core outcome measurement sets for clinical trials: OMERACT filter 2.0. *Journal of Clinical Epidemiology*, *67*(7), 745–753. https://doi.org/10.1016/j.jclinepi.2013.11.013

Castrejon, I., & Pincus, T. (2012). Patient self-report outcomes to guide a treat-to-target strategy in clinical trials and usual clinical care of rheumatoid arthritis. *Clinical and Experimental Rheumatology*, *30*(4 Suppl. 73), S50–S55.

Chen, L., Deng, H., Cui, H., Fang, J., Zuo, Z., Deng, J., … Zhao, L. (2017). Inflammatory responses and inflammation-associated diseases in organs. *Oncotarget*, *9*(6), 7204–7218. https://doi.org/10.18632/oncotarget.23208

Chewning, B., Bylund, C. L., Shah, B., Arora, N. K., Gueguen, J. A., & Makoul, G. (2012). Patient preferences for shared decisions: A systematic review. *Patient Education and Counseling*, *86*(1), 9–18. https://doi.org/10.1016/j.pec.2011.02.004

de Wit, M. (2017). The patient perspective. In M. C. Hochberg, E. M. Gravallese, A. J. Silman, J. S. Smolen, M. E. Weinblatt, & M. H. Weisman (Eds.), *Rheumatology* (7th ed.) (pp. 409–412). Elsevier.

de Wit, M. P., Kvien, T. K., & Gossec, L. (2015). Patient participation as an integral part of patient-reported outcomes development ensures the representation of the patient voice: A case study from the field of rheumatology. *RMD Open*, *1*(1), 1–7, e000129. https://doi.org/10.1136/rmdopen-2015-000129

Dinarello, C. A. (2010). Anti-inflammatory agents: Present and future. *Cell*, *140*(6), 935–950. https://doi.org/10.1016/j.cell.2010.02.043

Ekman, I., Swedberg, K., Taft, C., Lindseth, A., Norberg, A., Brink, E., … Sunnerhagen, K. S. (2011). Person-centered care—Ready for prime time. *European Journal of Cardiovascular Nursing*, *10*(4), 248–251. https://doi.org/10.1016/j.ejcnurse.2011.06.008

Fautrel, B., Alten, R., Kirkham, B., de la Torre, I., Durand, F., Barry, J., … Taylor, P. C. (2018). Call for action: How to improve use of patient-reported outcomes to guide clinical decision making in rheumatoid arthritis. *Rheumatology International*, *38*(6), 935–947. https://doi.org/10.1007/s00296-018-4005-5

Felson, D. T., Anderson, J. J., Boers, M., Bombardier, C., Chernoff, M., Fried, B., … Lightfoot, R. (1993). The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. The Committee on Outcome Measures in Rheumatoid Arthritis Clinical Trials. *Arthritis and Rheumatism*, *36*(6), 729–740. https://doi.org/10.1002/art.1780360601

Felson, D. T., Smolen, J. S., Wells, G., Zhang, B., van Tuyl, L. H., Funovits, J., … Boers, M. (2011). American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. *Arthritis and Rheumatism*, *63*(3), 573–586. https://doi.org/10.1002/art.30129

Ferreira, R. J. O., Carvalho, P. D., Ndosi, M., Duarte, C., Chopra, A., Murphy, E., … da Silva, J. A. P. (2019). Impact of patient global assessment on achieving remission in patients with rheumatoid arthritis: A multinational study using the METEOR database. *Arthritis Care and Research*, *71*(10), 1317–1325. https://doi.org/10.1002/acr.23866

Ferreira, R. J. O., de Wit, M., Henriques, M., Pinto, A., Duarte, C., Mateus, E. F., … Ndosi, M. (2019). "It can't be zero!": Difficulties in completing patient global assessment in rheumatoid arthritis: A mixed-methods study. *Rheumatology*, 1–11. https://doi.org/10.1093/rheumatology/kez467

Ferreira, R. J. O., Dougados, M., Kirwan, J., Duarte, C., de Wit, M., Soubrier, M., … Gossec, L. (2017). Drivers of patient global assessment in patients with rheumatoid arthritis who are close to remission: an analysis of 1588 patients. *Rheumatology*, *56*(9), 1573–1578. https://doi.org/10.1093/rheumatology/kex211

Ferreira, R. J. O., Duarte, C., Ndosi, M., de Wit, M., Gossec, L., & da Silva, J. A. P. (2018). Suppressing inflammation in rheumatoid arthritis: Does patient global assessment blur the target? A practice-based call for a

paradigm change. *Arthritis Care and Research*, *70*(3), 369–378. https://doi.org/10.1002/acr.23284

Ferreira, R. J. O., Eugenio, G., Ndosi, M., Silva, C., Medeiros, C., Duarte, C., & da Silva, J. A. P. (2018). Influence of the different "patient global assessment" formulations on disease activity score by different indices in rheumatoid arthritis. *Clinical Rheumatology*, *37*(7), 1963–1969. https://doi.org/10.1007/s10067-018-4063-9

Ferreira, R. J. O., Gossec, L., Duarte, C., Nicklin, J. K., Hewlett, S., da Silva, J. A. P., & Ndosi, M. (2018). The Portuguese Rheumatoid Arthritis Impact of Disease (RAID) score and its measurement equivalence in three countries: Validation study using Rasch models. *Quality of Life Research*, *27*(11), 2909–2921. https://doi.org/10.1007/s11136-018-1959-4

Ferreira, R. J. O., Ndosi, M., de Wit, M., Santos, E. J. F., Duarte, C., Jacobs, J. W. G., … da Silva, J. A. P. (2018). Dual target strategy: A proposal to mitigate the risk of overtreatment and enhance patient satisfaction in rheumatoid arthritis. *Annals of the Rheumatic Diseases*, e109. https://doi.org/10.1136/annrheumdis-2018-214199

Ganesan, N. (2018). Adopting patient-reported outcomes in clinical care: Challenges and opportunities. Retrieved from https://avalere.com/insights/adopting-patient-reported-outcomes-in-clinical-care

Gossec, L., Dougados, M., & Dixon, W. (2015). Patient-reported outcomes as end points in clinical trials in rheumatoid arthritis. *RMD Open*, *1*(1), 1–6, e000019. https://doi.org/10.1136/rmdopen-2014-000019

Gossec, L., Dougados, M., Rincheval, N., Balanescu, A., Boumpas, D. T., Canadelo, S., … Kvien, T. K. (2009). Elaboration of the preliminary Rheumatoid Arthritis Impact of Disease (RAID) score: A EULAR initiative. *Annals of the Rheumatic Diseases*, *68*(11), 1680–1685. https://doi.org/10.1136/ard.2008.100271

Gruffydd-Jones, K. (2019). Unmet needs in asthma. *Therapeutics and Clinical Risk Management*, *15*, 409–421. https://doi.org/10.2147/TCRM.S160327

Harding, E., Wait, S., & Scrutton, J. (2015). The state of play in person centred care: A pragmatic review of how person-centred care is defined, applied and measured, featuring selected key contributors and case studies across the field. Retrieved from http://www.healthpolicypartnership.com/wp-content/uploads/State-of-play-in-person-centred-care-full-report-Dec-11-2015.pdf

Huber, M., Knottnerus, J. A., Green, L., van der Horst, H., Jadad, A. R., Kromhout, D., … Smid, H. (2011). How should we define health? *BMJ (Clinical Research Ed.)*, *343*, d4163. https://doi.org/10.1136/bmj.d4163

Jacobs, B. M., Giovannoni, G., & Schmierer, K. (2018). No evident disease activity—More than a risky ambition? *JAMA Neurology*, *75*(7), 781–782. https://doi.org/10.1001/jamaneurol.2018.0829

Kiely, P. D. W., & Nikiphorou, E. (2018). Management of rheumatoid arthritis. *Medicine*, *46*(4), 216–221. https://doi.org/10.1016/j.mpmed.2018.01.006

Komatsu, H., & Yagasaki, K. (2014). The power of nursing: Guiding patients through a journey of uncertainty. *European Journal of Oncology Nursing*, *18*(4), 419–424. https://doi.org/10.1016/j.ejon.2014.03.006

Larsson, I. (2013). Person-centred care in rheumatology nursing in patients undergoing biological therapy: An explorative and interventional study. (Doctoral thesis), Jönköping University, Jönköping. Retrieved from http://hj.diva-portal.org/smash/get/diva2:615475/FULLTEXT02.pdf

McCormack, B., Borg, M., Cardiff, S., Dewing, J., Jacobs, G., Janes, N., … Wilson, V. (2015). Person-centredness—The "state" of the art. *International Practice Development Journal*, *5*(Suppl. 1), 1–15.

Meleis, A. I. (2010). Role insufficiency and role suplementation: A conceptual framework. In A. I. Meleis (Ed.), *Transitions theory: Middle range and situation specific theories in nursing research and practice* (pp. 13–24). New York, NY: Springer Publishing Company.

Meleis, A. I. (2018). *Theoretical nursing: Development and progress* (6th ed.). Philadelphia, PA: Kolters Kluever Health.

Nelson, E. C., Eftimovska, E., Lind, C., Hager, A., Wasson, J. H., & Lindblad, S. (2015). Patient reported outcome measures in practice. *BMJ*, *350*, g7818. https://doi.org/10.1136/bmj.g7818

Nicklin, J., Cramp, F., Kirwan, J., Urban, M., & Hewlett, S. (2010). Collaboration with patients in the design of patient-reported outcome measures: Capturing the experience of fatigue in rheumatoid arthritis. *Arthritis Care and Research*, *62*(11), 1552–1558. https://doi.org/10.1002/acr.20264

Oppenauer, C., Durechova, M., Zauner, M., Posch, M., Urach, S., Machold, K., … Stamm, T. (2019). Initial evidence for the need of a dual treat-to-target strategy in patients with rheumatoid arthritis [abstract]. *Annals of the Rheumatic Diseases*, *78*(Suppl. 2), 1118–1119. https://doi.org/10.1136/annrheumdis-2019-eular.3282

Philpot, L. M., Barnes, S. A., Brown, R. M., Austin, J. A., James, C. S., Stanford, R. H., & Ebbert, J. O. (2018). Barriers and benefits to the use of patient-reported outcome measures in routine clinical care: A qualitative study. *American Journal of Medical Quality*, *33*(4), 359–364. https://doi.org/10.1177/1062860617745986

Porter, I., Goncalves-Bradley, D., Ricci-Cabello, I., Gibbons, C., Gangannagaripalli, J., Fitzpatrick, R., … Valderas, J. M. (2016). Framework and guidance for implementing patient-reported outcomes in clinical practice: Evidence, challenges and opportunities. *Journal of Comparative Effectiveness Research*, *5*(5), 507–519. https://doi.org/10.2217/cer-2015-0014

Salisbury, C., Man, M. S., Bower, P., Guthrie, B., Chaplin, K., Gaunt, D. M., … Mercer, S. W. (2018). Management of multimorbidity using a patient-centred care model: A pragmatic cluster-randomised trial of the 3D approach. *Lancet*, *392*(10141), 41–50. https://doi.org/10.1016/s0140-6736(18)31308-4

Santos, E. F., Duarte, C. M., Ferreira, R. O., Pinto, A. M., Geenen, R., & da Silva, J. P. (2019). Multifactorial explanatory model of depression in patients with rheumatoid arthritis: A structural equation approach. *Clinical and Experimental Rheumatology*, *37*(4), 641–648.

Santos, E. J. F., Duarte, C., Marques, A., Cardoso, D., Apostolo, J., da Silva, J. A. P., & Barbieri-Figueiredo, M. (2019). Effectiveness of non-pharmacological and non-surgical interventions for rheumatoid arthritis: An umbrella review. *JBI Database of Systematic Reviews and Implementation Reports*, *17*(7), 1494–1531. https://doi.org/10.11124/jbisrir-d-18-00020

Santos, E. J. F., Duarte, C., da Silva, J. A. P., & Ferreira, R. J. O. (2019). The impact of fatigue in rheumatoid arthritis and the challenges of its assessment. *Rheumatology*, *58*(Suppl 5), v3–v9. https://doi.org/10.1093/rheumatology/kez351

Santos, E. J. F., Duarte, C., Ferreira, R. J. O., Pinto, A. M., Geenen, R., & da Silva, J. A. P. (2018). Determinants of happiness and quality of life in patients with rheumatoid arthritis: A structural equation modelling approach. *Annals of the Rheumatic Diseases*, *77*(8), 1118–1124. https://doi.org/10.1136/annrheumdis-2017-212934

Schultze, J. L., & Rosenstiel, P. (2018). Systems medicine in chronic inflammatory diseases. *Immunity*, *48*(4), 608–613. https://doi.org/10.1016/j.immuni.2018.03.022

Shaul, M. P. (2010). Transitions in chronic illness: Rheumatoid arthritis in women. In A. I. Meleis (Ed.), *Transitions theory: Middle range and situation specific theories in nursing research and practice* (pp. 361–370). New York, NY: Springer Publishing Company.

Silva, C. F. R., Duarte, C., Ferreira, R. J. O., Santos, E., & da Silva, J. A. P. (2019). Depression, disability and sleep disturbance are the main explanatory factors of fatigue in rheumatoid arthritis: A path analysis model. *Clinical and Experimental Rheumatology*.

Sousa, F. I. M., Santos, E. J. F., Cunha, M., Ferreira, R. J. O., & Marques, A. A. (2017). Effectiveness of nursing consultations in people with rheumatoid arthritis: Systematic review. *Revista de Enfermagem Referência*, *IV*(13), 147–156. https://doi.org/10.12707/RIV17013

Talib, T. L., DeChant, P., Kean, J., Monahan, P. O., Haggstrom, D. A., Stout, M. E., & Kroenke, K. (2018). A qualitative study of patients'

perceptions of the utility of patient-reported outcome measures of symptoms in primary care clinics. *Quality of Life Research*, *27*(12), 3157–3166. https://doi.org/10.1007/s11136-018-1968-3

Taylor, P. C., Moore, A., Vasilescu, R., Alvir, J., & Tarallo, M. (2016). A structured literature review of the burden of illness and unmet needs in patients with rheumatoid arthritis: A current perspective. *Rheumatology International*, *36*(5), 685–695. https://doi.org/10.1007/s00296-015-3415-x

Torres-González, F., Ibanez-Casas, I., Saldivia, S., Ballester, D., Grandón, P., Moreno-Küstner, B., … Gómez-Beneyto, M. (2014). Unmet needs in the management of schizophrenia. *Neuropsychiatric Disease and Treatment*, *10*, 97–110. https://doi.org/10.2147/NDT.S41063

Turner-Stokes, L. (2009). Goal attainment scaling (GAS) in rehabilitation: A practical guide. *Clinical Rehabilitation*, *23*(4), 362–370. https://doi.org/10.1177/0269215508101742

van Tuyl, L. H., Smolen, J. S., Wells, G. A., Scholte-Voshaar, M., Hoogland, W., & Boers, M. (2011). Patient perspective on remission in rheumatoid arthritis. *Journal of Rheumatology*, *38*(8), 1735–1738. https://doi.org/10.3899/jrheum.110394

van Tuyl, L. H. D., & Boers, M. (2017). Rheumatoid arthritis: Remission—Keeping the patient experience front and centre. *Nature Reviews. Rheumatology*, *13*(10), 573–574. https://doi.org/10.1038/nrrheum.2017.139

Ventura, F. (2016). Person-centred e-support: Foundations for the development of nursing interventions in outpatient cancer care. (Doctoral thesis), University of Gothenburg, Gothenburg. Retrieved from http://hdl.handle.net/2077/39524

Vinall-Collier, K., Madill, A., & Firth, J. (2016). A multi-centre study of interactional style in nurse specialist- and physician-led rheumatology clinics in the UK. *International Journal of Nursing Studies*, *59*, 41–50. https://doi.org/10.1016/j.ijnurstu.2016.02.009

Voshaar, M. J., Nota, I., van de Laar, M. A., & van den Bemt, B. J. (2015). Patient-centred care in established rheumatoid arthritis. *Best Practice and Research. Clinical Rheumatology*, *29*(4–5), 643–663. https://doi.org/10.1016/j.berh.2015.09.007

Weldring, T., & Smith, S. M. S. (2013). Patient-reported outcomes (PROs) and patient-reported outcome measures (PROMs). *Health Services Insights*, *6*, 61–68. https://doi.org/10.4137/HSI.S11093

How to cite this article: Ferreira RJO, Santos EJF, de Wit M, et al. Shared decision-making in people with chronic disease: Integrating the biological, social and lived experiences is a key responsibility of nurses. *Musculoskeletal Care*. 2019;1–8. https://doi.org/10.1002/msc.1443

Chapter VI

OVERVIEW AND FUTURE DIRECTIONS

OVERVIEW AND FUTURE DIRECTIONS

The work presented in this thesis is dedicated to the representation of the patient's perspective in the current paradigms of assessment and management of rheumatoid arthritis (RA), with special focus on the patient global assessment of disease activity (PGA).

We believe that several major contributions have been made:

1) we have provided strong support to the concept that the reliable application of PGA would require appropriate standardization of its formulation and formal education of patients regarding its construct and intended use;
2) we have contributed to the recognition that a high proportion of patients worldwide failed to achieve the Boolean-based remission, endorsed by the American College of Rheumatology (ACR) and by the European League Against Rheumatism (EULAR), solely due to a PGA >1 cm (0 to 10 cm) – PGA-near-remission. This status, which exposes patients to the risk of immunosuppressive overtreatment, is almost twice as frequent as "full" remission. These data firmly demonstrated that abrogation of the inflammatory process does not equate to abolition of the disease impact upon the patient;
3) we have provided further evidence that PGA is not a good representation of inflammatory disease activity as it correlates much more strongly with dimensions largely independent of inflammation: fatigue, pain, function and psychological features. We demonstrated, for the first time, that this dissociation between PGA and inflammation is almost absolute when patients are in a state near to remission, precisely when treatment decisions are more often and decisive;
4) we have demonstrated that PGA has no significant influence on the progression of radiographic damage in patients who are otherwise in remission. We also added significantly to the evidence demonstrating a mismatch between remission and functional status, even if, as expected, the correlation with PGA is stronger in the functional domain;
5) taken together, the evidence above demonstrates that PGA
    a. does, in fact, blur the clinical target currently used to guide the management RA management,
    b. is not appropriate to support decisions regarding immunosuppressive therapy, at least in the low levels of disease activity,

    thus questioning a deep-rooted current paradigm;
6) we, therefore, proposed a novel "dual target approach" to the management of RA, reconciling a sharpened clinical target, focused on the inflammatory process (3v-

remission) and highlighting a separate patient target, focused on the impact of the disease upon the patient's life.

7) we explored the outreach of our observations in RA to the wider realm of chronic disease management. To this purpose we are in the final stages of designing and proposing a model aimed at reconciling clinical and patient goals, through the use of Patient-Reported Outcomes and defined personal goals, in the context of a multi-professional team, with a decisive contribution by the nurse.

We are fully aware that these may be seen as rather bold statements, with potentially very ambitious implications in the field and (perhaps unwarranted but) "courageous" questioning of widely accepted paradigms established by authoritative bodies. We are glad to embrace that responsibility as our aims were, from the start, to contribute to change towards a stronger representation of the patient's perspective in the management of RA. This, naturally, calls for a rigorous scrutiny of the quality of the evidence we have produced.

There is, surely, no research without weakness and limitations. We have consistently addressed them in each of the papers and these were considered by co-authors, peer-reviewers and journal editors. The scope of journals that accepted our full papers and letters provides, we believe, reasonable reassurance regarding the appropriateness of the methods, the validity of the results and of their interpretation. We have also tried to assure the robustness of the overall body of work, by using different sources of data and methods of analysis in different studies. The scope is quite varied, from local and national to international and even worldwide databases, data from cross-sectional and prospective cohorts, from observational studies and randomized controlled clinical trials, from early to established RA. Methods included qualitative and quantitative studies, uni- and multivariate analyses, meta-analysis of individual patient data, among others. During all this process we paid very close attention to publications and oral presentations in the field and adapted our views and projects to the evolving evidence.

Also aware that changing the field would require robust evidence, it was decided, from the start, to try and engage internationally eminent researchers in the field of rheumatology and nursing (supervisors included), as well as active patient research partners. This strategy aimed not only at improving the quality of the studies, through critical advice at all stages, from study design to data analysis and interpretation, but also to potentiate the educational benefit for the PhD student and the impact of the work in international guiding bodies, ultimately aiming at changing the outcomes for patients. We learned an enormous amount of science and wisdom from our co-authors and we are extremely grateful for that. Despite all this, we are sure that our work will be critically revised, eventually contradicted and refined

through additional research in our group and others. That is the natural path of science.

The short description of the scope of methods and contributors presented above also conveys the immense variety of opportunities that this work provided to the personal and professional development of the PhD candidate. Of the many new skills that had to be acquired during this process, the use of the SAS and STATA statistical package, the learning of the Rasch analysis methodology using RUMM2030 software (for work not included in the body of this thesis), cleaning very big longitudinal databases (using excel, among other tools) as well as randomized controlled trials' (RCTs) databases, which are very different, working in online secure platforms used in the data management of RCTs, deserve being highlighted. Some personal qualities had also to be developed, with emphasis on team work, international networking skills, critical thinking, rigorous appraisal of methods and evidence and resilience – manuscript 10, for instance, took the last 18 months to reach the current status, but a total of >30 months since the start of the data request to the trial's sponsors. Our commitment to research and an academic career received, altogether, a powerful boost.

The potential reach and impact of the work included in this thesis is, we believe, very stimulating. We hope that the evidence and proposals produced may be widely recognized and influence the scientific committees responsible for updating the treat-to-target strategy and the treatment recommendations. This would be a decisive step in inspiring health professionals around the world to change their practice, reinforce person-centered care and, thus, improve patients' lives.

We do believe that the evidence and arguments we have produced deserve this level of attention and impact upon the current treatment paradigms. In fact, the contributions summarized in the beginning of this section are, in our view, a strong argument towards the adoption of the dual-target approach at the highest level. We see two major reasons for this:

- PGA is not related to the inflammatory process once patients are otherwise in remission. Patients in PGA-near-remission, a considerable proportion in practice as we demonstrated, cannot expect to see their situation improved by reinforced immunosuppression, as indicated in strict adherence to current recommendations. There is no inflammatory activity to be reduced, no impact that depends on inflammation and, as we demonstrated for the first time, no gain in terms of structural damage.

Therefore, these patients are exposed to the additional risks of overtreatment, without any expected gains in efficacy. Moreover, if PGA is kept in the definition of target physicians may consider that the patient's perspective is already dully incorporated and reflected in the treatment guidelines. This is obviously not the case, as full control of the inflammatory

process does not equate to abrogation of the impact of disease upon the patient, as reflected by the large proportion of patients in PGA-near-remission.

- The impact of the disease in patients' lives needs to be central to the treatment objectives and management strategy. Although control of the inflammatory process is a major contribution to improve the quality of life, once this is achieved patients who still have relevant impact of the disease need adjunctive measures to address the domains underlying the persisting impact, not additional immunosuppression.

The selection of these measures requires that impact is assessed by tools that are discriminative enough to appropriately guide the choice in a personalized way. A high PGA does not discriminate the underlying reasons of the disease impact, which can arise from pain to emotional well-being or disturbed sleep, among other origins. Studies designed to determine the best instruments that can be used to serve this purpose are, naturally, needed. It seems, however, mandatory to conclude that a second target, focused on patients' needs, must be kept in mind if we are to provide each patient with the best possible outcomes.

Contrary to arguments expressed by Lilian van Tuyl and Maarten Boers regarding our work,[1] [2] our proposal does not diminish the representation of patients' views in the target guiding therapy, it actually highlights and reinforces them by demanding that patient goals are reliably and independently represented in the target and in the tight control along the treatment path.

The best practical demonstration of the value of the dual-target approach is given, to date, by a study performed in Vienna, in which we were invited to collaborate. This study explored if achieving RA's biological remission, as by Clinical Disease Activity Index (CDAI), equated to achieve individual patient treatment goals. Among the 101 patients with a follow-up of three to five months, 44% achieved both targets while 17% failed both. Around one fifth of the patients achieved only their personal goals while another fifth achieved only the biological target.[3] These results support the need of a dual strategy, supplementing the medical treatment with management geared towards individual goals.

We do believe that the already preeminent work of nurses in rheumatology care could and should be expanded to reassure that the patients' perspectives and needs are dully recognized and integrated in the management plan conducted by the multi-professional team. This would entail considerable work educating patients on the meaning and use of patient-reported outcome measures (PROMs) but also on devising individually tailored treatment goals. These tasks are very close to the professional philosophy and core competencies of nurses. Nurses contributions ought to be harmonized and combined with the competencies of other health professionals, especially the technical abilities of

physicians, naturally more focused on the disease process, to provide patients with the best possible experience with the disease and optimal long-term outcomes. We have explored the possibility that a similar model may be applicable to a variety of other chronic conditions and look forward to the debate of that proposal by the scientific and clinical community.

Naturally the merit of the proposal above is not solely ours, as they rely in a vast array pre-existing and contemporary publications from a large number of groups and researchers. Their consideration by scientific committees will surely require addressing controversial views on these and other relevant data, and demand careful maturation of concepts, implications and consensus.

The fact that Ricado´s work has already resulted in the invitation to become a member of some influential governing bodies, such as the EULAR Standing Committee of Health Professionals in Rheumatology, or to become fellow in the working group on "Remission in RA-patient perspective" of the Outcome Measures in Rheumatology (OMERACT) consortium, is a promising sign.

Additional evidence will be needed to fill some relevant knowledge gaps.

Future research and prospects

Is PGA-near-remission associated with subclinical inflammation?

Despite our research it is still reasonable to admit that patients in PGA-near remission actually reflect, in their PGA score, persisting inflammation that is relevant to their well-being but is unrecognized by the clinical assessment. This inflammation could located at examined joints, but also in other joints not typically included in disease activity scores (e.g., feet joints) or in peri-articular tissues. This could be relevant not only to explain the PGA score but also to inform concerns regarding long-term radiological progression and systemic consequences of chronic inflammation. This hypothesis is somewhat contradicted by the demonstration that an US-based remission target does not lead to better outcomes than a clinically based one, despite increased treatment and related toxicity.[4 5 6] However, a full clarification of this issue would best be served by a dedicated ultrasound study comparing patients in different states of remission. One such study is underway with participants from the CoimbRA cohort.

What is the best possible definition of remission to predict good radiographic outcome in RA? Also*, does this vary depending on the treatment regimen?*

The results of our analysis of individual patients data from recent RCTs (**Manuscript 10**)

demonstrate that the performance of remission at 6 or 12 months as a predictor of radiographic damage progression in the subsequent 12 months is surprisingly poor. This has prompted us to consider that two lines of research are warranted to clarify this issue:

- Do the LRs vary according to the medication being used? (Hypothesis: Biological treatment is associated with better radiographic outcomes even if remission is not achieved)
- What is the best predictor of good radiographic outcome: Sustained remission? How to define “sustained”, Concomitant disease activity? Biological markers?

As stated in the protocol (**Manuscript 9**) we have plans to address some of these issues with the data from the RCTs.

With great interest we read also two recent studies developing and testing new tool to assess clinical remission excluding (for different reasons) the PROMs. Agustin and colleagues developed and validated a clinical ultrasound index, using a mixed-methods study, which resulted in a tool that sums the number of swollen joint counts, an ultrasonography qualitative score and CRP.[7] Gul and colleagues[8] studied a "multi-dimensional remission" defined as: clinical (tender and swollen joints in 28, C-reactive protein, all ≤1), ultrasound remission (total power doppler = 0) and immunological (T cell remission, i.e. positive normalized naive T-cell frequency).

Which instrument(s) are best suited to evaluate the disease impact and guide management of the patient target?

Several instruments are available that provide a multidimensional evaluation of the impact of disease (e.g. the "Rheumatoid Arthritis Impact of Disease" score, RAID[9]; the "Routine Assessment of Patient Index Data 3" score, RAPID 3[10]; the Flare Assessment in Rheumatoid Arthritis questionnaire, FLARE[11]; or the oldest Arthritis Impact Measurement Scales Health Status Questionnaire, AIMS2[12]), as needed to guide selection of adjuvant interventions. All of them have been validated, however, as single combined score and group (and not individual) level.

Studies need to be conducted to evaluate these tools or develop new ones to serve the stated objectives at the individual levels. Our group is currently conducting studies on the RAID with contribution by the author of this thesis.[9]

What interventions are available to improve the impact of disease in RA, beyond disease process control?

The use of adjunctive measures in RA has not received major attention over the years. The evidence available must be collected and structured in order to guide interventions and additional research. Work in this direction is underway in our group.[13]

Does a dual-target approach result in improved outcomes to the patient?

This question will require a pragmatic randomized clinical trial, based on a previous definition of appropriate outcomes and interventions. Several difficulties can be anticipated in the design and performance of such a study but its need and value seem rather obvious.

Personal prospects

The work described in the thesis has impacted profound changes to my technical and soft competencies , my ability to seek and provide international cooperation , my confidence and commitment to research and academia . I intend to continue along this path, deepening our research skills and contributions and inspiring young researchers and students to support the scientific community's efforts towards improving the quality of life as much as the longevity of our patients.

I want to keep involved in clinical work, the shortest-term goal being to test and implement the model of shared care described above, in the Rheumatology Department of Centro Hospitalar e Universitário de Coimbra where I work. This will involve the establishment of a nursing consultation for patients with chronic inflammatory arthritis, to add to the recently implemented Nursing Fracture Liaison Service. This project is supported by the Head of Department and was welcomed by the Hospital's Nursing Governing Body. Its successful implementation will, hopefully, foster the development of other similar units.

I intend to continuously develop my academic career at a local, national and international level. I have already, together with our nursing colleague Andréa Marques, submitted a proposal for a "Nursing Postgraduate Course in Chronic Inflammatory Diseases" to the Nursing School of Coimbra, which has passed the first step within the approval process.

I have been recently invited to the faculty team of the "I EULAR Postgraduate Course for Health Professionals in Rheumatology", and to teach "Statistical Methods" in a Portuguese Nursing School, among other collaborations and opportunities. Through involvement in international networks, I hope to foster person-centered care and the development of nursing as a clinical and a scientific profession.

Final comments

The final objective of treatment, in any field of Health Sciences, must be centered in the patient's experience of the disease, considering his/her overall life context. This paradigm has triggered a growing interest in the development and validation of patient-reported outcome measures. This work was focused in this field, as it aimed to contribute towards a greater impact of the patient's perspective upon the choice of management strategies, promoting wider-scope possibilities beyond the "simple" inclusion of a "global" PROM in the tools designed to guide medical treatment.

The ultimate aim resided in helping to foster more personalized and tailored care, based on shared decision-making (person-centered care), as a means to improve patients' health and enjoyment of life.

It was in thinking about the patient that we started to consider and develop these studies. When we propose refining the clinical target used by the physician, by taking a PROM away, we hope to improve the patient's outcome through better clinical decisions. When we suggest that the patients' perspective deserves a discriminative and separate outcome measure, we are trying to increase its specific weight on the decision-making process, and making sure that relevant personal goals are pursued and met. The role of the nurse is essential to bridge both actors and, ultimately, promote higher patient's satisfaction, better quality of life and happiness.

REFERENCES

1. van Tuyl LHD, Boers M. Rheumatoid arthritis: Remission - keeping the patient experience front and centre. Nat Rev Rheumatol 2017;13(10):573-74.

2. van Tuyl LHD, Boers M. The controversy of using PGA to define remission in RA. Nat Rev Rheumatol 2018;14(4):245.

3. Oppenauer C, Durechova M, Zauner M, et al. Initial evidence for the need of a dual treat-to-target strategy in patients with rheumatoid arthritis [abstract]. Ann Rheum Dis 2019;78(Suppl 2):1118-19.

4. Dale J, Stirling A, Zhang R, et al. Targeting ultrasound remission in early rheumatoid arthritis: the results of the TaSER study, a randomised clinical trial. Ann Rheum Dis 2016;75(6):1043-50.

5. Møller-Bisgaard S, Hørslev-Petersen K, Ejbjerg B, et al. Effect of Magnetic Resonance Imaging vs Conventional Treat-to-Target Strategies on Disease Activity Remission and Radiographic Progression in Rheumatoid Arthritis: The IMAGINE-RA Randomized Clinical Trial. JAMA 2019;321(5):461-72.

6. Haavardsholm EA, Aga A-B, Olsen IC, et al. Ultrasound in management of rheumatoid arthritis: ARCTIC randomised controlled strategy trial. BMJ 2016;354:i4205.

7. de Agustin JJ, Erra A, Ponce A, et al. Measuring inflammation in rheumatoid arthritis with a new clinical and ultrasound index: development and initial validation. Rheumatol Int 2019.

8. Gul HL, Eugenio G, Rabin T, et al. Defining remission in rheumatoid arthritis: does it matter to the patient? A comparison of multi-dimensional remission criteria and patient reported outcomes. Rheumatology (Oxford) 2019.

9. Ferreira RJO, Gossec L, Duarte C, et al. The Portuguese Rheumatoid Arthritis Impact of Disease (RAID) score and its measurement equivalence in three countries: validation study using Rasch Models. Qual Life Res 2018;27(11):2909-21.

10. Pincus T, Yazici Y, Bergman MJ. RAPID3, an index to assess and monitor patients with rheumatoid arthritis, without formal joint counts: similar results to DAS28 and CDAI in clinical trials and clinical care. Rheum Dis Clin North Am 2009;35(4):773-8, viii.

11. Berthelot JM, De Bandt M, Morel J, et al. A tool to identify recent or present rheumatoid arthritis flare from both patient and physician perspectives: the 'FLARE' instrument. Ann Rheum Dis 2012;71(7):1110-6.

12. Meenan RF, Mason JH, Anderson JJ, et al. AIMS2. The content and properties of a revised and expanded Arthritis Impact Measurement Scales Health Status Questionnaire. Arthritis Rheum 1992;35(1):1-10.

13. Santos EJF, Duarte C, Marques A, et al. Effectiveness of non-pharmacological and non-surgical interventions for rheumatoid arthritis: an umbrella review. JBI Database System Rev Implement Rep 2019;17(7):1494-531.

OTHER PUBLICATIONS ON THE TOPIC

Santos, E., Duarte, C., da Silva, J., & Ferreira, RJO. The impact of fatigue in rheumatoid arthritis and the challenges of its assessment. *Rheumatology (Oxford).* 2019 *Nov* 1;58 *(Supplement_5):v*3-*v*9*. doi:* 10.1093/*rheumatology*/*kez*351*.*

Silva CFR, Duarte C, Ferreira RJO, Santos E, da Silva JAP. Depression, disability and sleep disturbance are the main explanatory factors of fatigue in rheumatoid arthritis: a path analysis model. Clin Exp Rheumatol. 2019 Jul 19; [Epub ahead of print]

Bech B, Primdahl J, van Tubergen A, et al. 2018 update of the EULAR recommendations for the role of the nurse in the management of chronic inflammatory arthritis. Ann Rheum Dis. 2019 Jul 12;. doi: 10.1136/annrheumdis-2019-215458. [Epub ahead of print]

Santos EF, Duarte CM, Ferreira RJO, Pinto AM, Geenen R, da Silva JP. Multifactorial explanatory model of depression in patients with rheumatoid arthritis: a structural equation approach. Clin Exp Rheumatol. 2018 Jul-Aug;37(4):641-648.

Santos EJF, Duarte C, Ferreira RJO, Pinto AM, Geenen R, da Silva JAP. Determinants of happiness and quality of life in patients with rheumatoid arthritis: a structural equation modelling approach. Ann Rheum Dis. 2018 Aug;77(8):1118-1124. doi: 10.1136/annrheumdis-2017-212934.

Ferreira RJO, Gossec L, Duarte C, Nicklin JK, Hewlett S, da Silva JAP, Ndosi M. The Portuguese Rheumatoid Arthritis Impact of Disease (RAID) score and its measurement equivalence in three countries: validation study using Rasch Models. Qual Life Res. 2018 Nov;27(11):2909-2921. doi: 10.1007/s11136-018-1959-4.

Sousa FIM, Santos EJF, Cunha M, Ferreira RJO, Marques AM. Efectiveness of nursing consultations in people with rheumatoid arthritis: systematic review. Revista de Enfermagem Referência 2017;IV(13):147-56.

CURRICULUM VITAE

Ricardo Jorge de Oliveira Ferreira, MSc is a Registered Nurse at the Rheumatology Department of the Centro Hospitalar e Universitário de Coimbra, Portugal.

Mr. Ferreira graduated from the Nursing School of Coimbra in 2003, and three years later obtained his master's degree in Health Sociopsychology from the Instituto Superior Miguel Torga, Coimbra. Currently waiting for the defense of his PhD thesis on the "Impact of Patient Reported Outcomes in Rheumatoid Arthritis' Assessment and Management", Mr Ferreira's research interests include the determinants of quality of life in patients with rheumatoid arthritis, patient-reported outcomes, health literacy, remission definition, and patient educational needs in rheumatology. Mr. Ferreira has authored more than 30 peer-reviewed articles and four book chapters. He has been an invited speaker and Chair at many national and international meetings.

Mr. Ferreira was one of the founders and the first vice president of Portuguese Association Health Professionals in Rheumatology (APPSReuma), has been an active member of the European League Against Rheumatism (EULAR) since 2013 and is currently the Chair Elected of the EULAR Standing Committee of Health Professionals in Rheumatology. He has contributed to the development of several guidelines for clinical practice, including guidelines for monitoring comorbidities in inflammatory rheumatic diseases, and for the education of people with inflammatory arthritis, and more recently, to the update of the EULAR recommendations for the role of the nurse in the management of chronic inflammatory arthritis. Currently, he is working on the national implementation of these guidelines. He is a member of the editorial board of Rheumatology Advances in Practice (Oxford) and a reviewer for several other rheumatology journals, including the Arthritis Care & Research, the Acta Reumatológica Portuguesa, or the Nursing Journal Referência.

ACKNOWLEDGEMENTS

Designing, conducting and concluding this study would not have been possible without the help of many people, to whom I express my deepest gratitude.

In this context, I would like to especially thank:

- Professor José António Pereira da Silva, MD, PhD, for being my thesis supervisor, scientific mentor and friend. His energy, dedication, passion, vision, enthusiasm, leadership, among several other qualities, brought me into rheumatology field and allowed me to fully enjoy a journey of which I am very proud of. Our weekly meetings, with long discussion, pursuing the highest standards, as well as his patience, pedagogic skills, and empathy in a few difficult moments were essential to achieve this endeavor.

- Professor Laure Gossec MD, PhD, for her positive energy, trust, guidance, support, and balance brought into this work. Her generosity, kindness, efficiency, as well as integrity, were also qualities that I appreciated so much. The two weeks working together were very important to improve, among others, my writing skills and critical thinking. I returned much more inspired and confident on the journey we accomplished so far, that for sure will continue.

- Professor Mwidimi Ndosi, RN, PhD, for his continuous support, no matter what if at night or weekends, for the scientific and nursing mentoring, humor, and friendship. The two weeks in Bristol were also very much inspirational to me, and the good coffee was essential to keep me alert during the long days we spent doing Rasch analyses. I thank also for the friendly guidance not only within the work of this thesis but also, and very importantly, in the wider scope of Rheumatology and Nursing.

- To Professor Manuel Rodrigues, for being my "thesis's tutor", for contributing decisively to the existence and quality of this Nursing Doctoral Programme, as well as for being my friend and professional role model.

- To my closest Department's colleagues Andréa Marques, Cátia Duarte and Maria João Salvador, as well as to Eduardo Santos, who joined latter, for the support and contribution to this work, other inspirational and challenging projects together, and mainly for being my friends, with all it encloses. To Catia I express my deepest gratitude for her essencial contribution for the initial conception of this project and continuous support.

- To all rheumatologists, nurses, secretariat staff from Coimbra's Rheumatology department for the generous collaboration in data collection for this work, scientific and clinical discussions, as well as for having received me so well and make me part of this fantastic team, which also includes the healthcare auxiliary services staff.

- To all my co-authors, with a special recognition to Paco Welsing, for his expertise and support, without whom the IPD Meta-analysis project would have been simply impossible to conclude. My first week in Utrecht, with first contact to SAS was probably the hardest one.

- To the Master's students who were involved in this project, for their interest, collaboration in data collection, analysis and discussion, and in some cases in manuscripts preparation.

- To all the patients who kindly accepted to collaborate in these research studies.

- To António Marques (former Nursing Director, currently my Department's Supervisor) and to Áurea Andrade (Nursing Director) who believed in this project and continuously supported it. I am looking forward for continuing of our projects such as the implementation of a nursing consultation.

- To Professor Helena Canhão and Professor Loreto Carmona, that although not being co-authors, kindly reviewed and discussed some of our studies and ideas.

- To Jos van der Velden (SAS, Portugal) for his kind and competent and generous support in the introduction to SAS.

- To all my family, especially to my godfather Jorge for his deepest support to all my activities since I was a child.

- To my beloved parents and brother, for their unconditional love, support, and decisive role on my education.

- To all my closest friends, luckily a lot, thus I do not have time (as you know) to write all your names

- To Ândrea for her love, happiness, support, and encouragement and to Gaspar, the center of my life.